A. M. A.

ARCHIVES OF

NEUROLOGY AND PSYCHIATRY

JANUARY 1952

VOLUME 67 NUMBER 1

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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THE A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system and to disseminate knowledge in this department of medicine.

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AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **CHICAGO 10**

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 67 JANUARY 1952 NUMBER 1

SEVERE SENSORY CHANGES, AND TROPHIC DISORDER, IN PERONEAL MUSCULAR ATROPHY (CHARCOT-MARIE-TOOTH TYPE)

A. C. ENGLAND, M.D.
AND
D. DENNY-BROWN, M.D.
BOSTON

THE EARLY descriptions of peroneal muscular atrophy failed to draw any clear distinction between this disease and the amyotrophic spinal disease called progressive spinal muscular atrophy, of which it was at first assumed to represent a familial form. The publication in 1886 of the classic commentaries of Charcot and Marie [1] and of Tooth [2] drew attention to the onset of the hereditary disease in childhood, its commencement in the feet and legs, the sparing of proximal muscles, and the occasional occurrence of mild sensory changes as distinguishing features. These features led Tooth to propose that peroneal muscular atrophy is an affection of the peripheral nerves, as opposed to primary affection of the anterior horn cells in progressive neural muscular atrophy. Charcot and Marie favored the possibility of a myelopathy. Hoffmann,[3] in presenting further cases, also emphasized the slight sensory changes and drew attention to the autopsy in a case described in 1855 by Virchow,[4] which revealed degeneration of the peripheral nerves, worse distally than proximally, and of the posterior roots and root ganglia, with changes in the anterior horn cells and dorsal columns of the spinal cord. Hoffmann proposed the name progressive neurotic muscular atrophy, evidently considering the disorder a degeneration of primary and sensory neurones. Bernhardt [5] again stressed the neuritic features which had impressed Tooth and proposed the term "spinal neuritic form of progressive muscular atrophy." Though the disease was known by this name in the subsequent German literature, various

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

1. Charcot, J. M., and Marie, P.: Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, débutant par les pieds et les jambes, et atteignant plus tard les mains, Rev. méd. **6**:97, 1886.

2. Tooth, H. H.: The Peroneal Type of Progressive Muscular Atrophy, London, H. K. Lewis & Co., Ltd., 1886.

3. Hoffmann, J.: Über progressive neurotische Muskelatrophie, Arch. Psychiat. **20**:660, 1889; Deutsche Ztschr. Nervenh. **6**:150, 1895.

4. Virchow, R.: Ein Fall von progressiven Muskelatrophie, Virchows Arch. path. Anat. **8**:537, 1855.

5. Bernhardt, M.: Weiterer Beitrag zur Lehre von den hereditären und familiären Erkrankungen des Nervensystems: Über die spinal-neuritische Form der progressiven Muskelatrophie, Virchows Arch. path. Anat. **133**:259, 1893.

French writers, notably Marinesco [6] and Sainton,[7] following Marie, continued to speak of the affection as a spinal disease. The emphasis on degeneration in the spinal cord appears to be due to the finding of a slight loss of anterior horn cells and of degeneration of the dorsal columns, although degeneration of dorsal nerve roots was also noted. In Sainton's case degeneration of the lateral column, of moderate degree, was recognized as being related to recent cerebral thrombosis. Cassirer and Maas,[8] in reporting an additional case with autopsy in 1910, introduced a further complication in their finding of chains of nuclei in sections of the atrophic muscles, as well as neuritic changes, and were led to propose that the disease was a "chronic neuromyositis." In more recent times, Wohlfahrt,[9] on the basis of biopsies in a typical family, dismissed the myositic changes but appeared to be convinced of the importance of degeneration in the lateral columns, described by others. Artom [10] presented a typical family, with autopsy in one case. He observed neural atrophy of the muscles, with degenerative changes in the peripheral nerves and increase in the endomysium. There were slight degeneration in the dorsal columns and slight reduction in the number of anterior horn cells. The lateral columns were intact in the lumbar region, but in the cervical region Weigert sections showed slight pallor in the middle of both lateral columns. After an excellent discussion of the findings of others, Artom also concluded that the disease was a "spinal neuritic" disorder.

The cases with autopsy, except those of Artom and Gierlich, have all been nonfamilial. The case of Gierlich [11] was somewhat atypical, in that the onset was in the second year of life, with death at the age of 10 years. There was no recorded sensory disorder. Gierlich found degeneration of the muscles, nerves, and motor nerve roots; doubtful degeneration of the dorsal nerve roots, and degeneration in the dorsal and lateral columns. A brother was affected with the same disease.

The existence of degeneration of the peripheral nerves and nerve roots in peroneal muscular atrophy appears, therefore, to be well founded. It is now accepted that degeneration of the dorsal columns may be expected in chronic peripheral neuritis, and the finding of degeneration in the dorsal root ganglia by Virchow [4] and in the dorsal nerve roots by Sainton,[7] Siemeerling [12] and Cassirer and Maas [8] appears to confirm this view of the origin of the disease. Doubt is raised by the reputed severity of the lesion in the dorsal column, in relation to the slight changes in the dorsal nerve roots, in the cases of Gierlich,[11] Dejerine

6. Marinesco, G.: Contribution à l'étude de l'amyotrophie Charcot-Marie, Arch. méd. expér. **6**:921, 1894.

7. Sainton, P.: L'amyotrophie type Charcot-Marie, Thesis, Paris, No. 422, G. Steinheil, 1899.

8. Cassirer, R., and Maas, O.: Beitrag zur pathologischen Anatomie der progressiven neurotischen Muskelatrophie, Deutsche Ztschr. Nervenh. **39**:321, 1910.

9. Wohlfahrt, S.: De l'amyotrophie progressive à type Charcot-Marie, Acta med. scandinav. **63**:195, 1925-1926.

10. Artom, G.: Sull'atrofia muscolare progressiva, tipo Charcot-Marie: Contributo clinico ed anatomico-patologico, Arch. gen. neurol., psichiat. e psicoanal. **1**:30, 1920.

11. Gierlich: Beitrag zur Pathologie der neuralen Muskelatrophie (Hoffmann), Arch. Psychiat. **45**:447, 1909.

12. Siemerling, E.: Zur Lehre der spinal neurotischen Muskelatrophie, Arch. Psychiat. **31**:105, 1898.

and Armand-Delille,[13] and Siemerling.[12] Many authors, including Wilson,[14] have therefore continued to consider a spinal-tract degeneration as a primary feature of the disease. An additional argument advanced in favor of a "spinal neuritic" pathology is the frequent absence of sensory symptoms and signs.

Considerable deviation in the features of the disease has been noted. The familial occurrence of thickened nerves, miosis, nystagmus, and sensory changes, in addition to the distal atrophy, is now usually considered to belong to the similar, but independent, syndrome of chronic hypertrophic interstitial polyneuritis of Dejerine and Sottas. Rare cases with involvement of the facial, shoulder-girdle and gluteal muscles raise a suspicion of facioscapulohumeral dystrophy. Reports of conditions which combine features of peroneal muscular atrophy with those of Friedreich's ataxia are less difficult to set aside. In such cases both severe progressive muscular atrophy and cerebellar signs, such as were found by Spiller,[15] Greenfield,[16] van Bogaert and Moreau,[17] and Ross,[18] have seldom been presented. The condition has had the appearance of distal amyotrophy of nonspecific type associated with Friedreich's ataxia in the same patient. More frequently and persistently, there have been reports of families showing "areflexia with pes cavus," with or without dysarthria and kyphoscoliosis, but without nystagmus or other true cerebellar signs. In such families, reported by Roussy and Lévy,[19] Symonds and Shaw,[20] Rombold and Riley,[21] Popow,[22] and van Bogaert and Borremans,[23] the disease has been characteristic neither of Friedreich's ataxia nor of peroneal muscular atrophy. Spillane,[24] however, has reported such a family, with 21 members, one of whom presented a syndrome considered typical of Friedreich's ataxia and three a syndrome characteristic of peroneal muscular atrophy. The family described by Spillane would appear to establish the mixture of these syndromes in various degrees; yet there are still several difficulties to be met before these diseases can be said to belong to the same pathological process. First, the

13. Dejerine and Armand-Delille: Un cas d'atrophie musculaire, type Charcot-Marie, suivi d'autopsie, Rev. neurol. **11**:1198, 1903

14. Wilson, S. A. K.: Neurology, Vol. 2, London, Edward Arnold & Co., 1940.

15. Spiller, W. G.: Friedreich's Ataxia, J. Nerv. & Ment. Dis. **37**:411, 1910.

16. Greenfield, J. G.: Case of Peroneal Atrophy with Signs of Friedreich's Disease, Proc. Roy. Soc. Med. **5**:75, 1911-1912.

17. van Bogaert, L., and Moreau, M.: Combinaison de l'amyotrophie de Charcot-Marie-Tooth et de la maladie de Friedreich, Encephale **34**:312, 1940.

18. Ross, A. T.: Combination of Friedreich's Ataxia and Charcot-Marie-Tooth Atrophy in Each of 2 Brothers, J. Nerv. & Ment. Dis. **95**:680, 1942.

19. Roussy, G., and Lévy, G.: Sept cas d'une maladie familiale particulière: troubles de la marche, pieds bots, et aréfléxie tendineuse généralisée, avec, accessoirement, légère maladresse des mains, Rev. neurol. **1**:427, 1926.

20. Symonds, C. P., and Shaw, M. E.: Familial Claw-Foot with Absent Tendon-Jerks: A "Forme Fruste" of the Charcot-Marie-Tooth Disease, Brain **49**:387, 1926.

21. Rombold, C. R., and Riley, H. A.: The Abortive Type of Friedreich's Disease, Arch. Neurol. & Psychiat. **16**:301 (Sept.) 1926.

22. Popow, A.: Une famille atteinte d'une forme particulière de maladie héréditaire (forme de Roussy-Lévy), Rev. neurol. **2**:447, 1932.

23. van Bogaert, L., and Borremans, P.: Étude d'une famille présentant le maladie familiale particulière de Roussy-Lévy (aréfléxie tendineuse et pieds bots), Rev. neurol. **2**:529, 1932.

24. Spillane, J. D.: Familial Pes Cavus and Absent Tendon-Jerks: Its Relationship with Friedreich's Disease and Peroneal Muscular Atrophy, Brain **63**:275, 1940.

natural history of the inevitably progressive ataxia of the Friedreich type differs radically from that of the slow, halting, and limited progress of peroneal muscular atrophy. Second, though the signs and symptoms of Friedreich's ataxia are distinctive, those of peroneal muscular atrophy can be differentiated from other chronic peripheral neuropathies only by the usual onset of the disorder in childhood, with resulting pes cavus, its familial incidence, and its slight sensory disturbance. If only the thickening of nerves, miosis, and nystagmus distinguish the hypertrophic interstitial neuritis of Dejerine and Sottas, it is still possible that familial peroneal atrophy, which may run true to type through very large families, such as those described by Herringham,[25] is distinct from the amyotrophic disorder which has been observed in association with Friedreich's disease.

The sensory changes in reported cases have been seldom severe. In one of the cases of Charcot and Marie (the nonfamilial case of "Sultz," in which Marinesco[6] later reported the autopsy findings) there were anesthesia to pinprick and thermal stimuli over the feet, with fading hypesthesia up to the level of the thighs. Many authors have spoken of slight sensory changes in the feet. De Lisi,[26] Davidenkoff,[27] and Biemond[28] mentioned sensory changes of moderate degree. Only Halliday and Whiting,[29] and Raymond,[30] besides Charcot, described severe sensory loss in the feet, and in some cases in the hands. In Halliday and Whiting's case a trophic ulcer of the foot had resulted. Only in such cases have shooting pains in the limbs, resembling lightning pains, been observed. Deformity resulting from muscular weakness, with cutaneous changes resulting from overinversion of the feet, have been commonly reported, but these, with the associated blueness and coldness of the feet, can undoubtedly occur without demonstrable sensory loss. The family which is the subject of the present report is presented primarily on account of the severe loss of sensation with true trophic lesions in some of the patients and the inferences which may be drawn from the pattern of sensory changes.

GENERAL DATA REGARDING THE L FAMILY

A patient with typical peroneal muscular atrophy (*V-51*) presented herself at the Boston City Hospital, with signs and symptoms which will be disclosed below. She reported that the disease had affected three of her sisters, a statement which proved to be true. It was fortunate that one of her distant relatives was keenly interested in genealogy and had accumulated a large amount of factual data on the family. She, in turn, produced the commentaries of Prof. A. E. Verrill, of Yale University.

25. Herringham, W. P.: Muscular Atrophy of the Peroneal Type Affecting Many Members of a Family, Brain **11**:230, 1899.

26. de Lisi, L.: Osservazioni e studi sulla trasmissione ereditaria dell'atrofia muscolare progressiva tipo Charcot-Marie, Riv. pat. nerv. **31**:390, 1926.

27. Davidenkoff, S.: Über die neurotische Muskelatrophie Charcot-Marie, klinisch-genetische Studien, Ztschr. ges. Neurol. u. Psychiat. **107**:259; **108**:344, 1927.

28. Biemond, A.: Neuritische Muskelatrophie und Friedreichsche Tabes in derselben Familie, Deutsche Ztschr. Nervenh. **104**:113, 1928.

29. Halliday, J. R., and Whiting, A. J.: The Peroneal Type of Muscular Atrophy, Brit. M. J. **2**:1114, 1909.

30. Raymond, F.: Leçons sur les maladies du système nerveux (année 1900-1901), Paris, O. Doin, 1903.

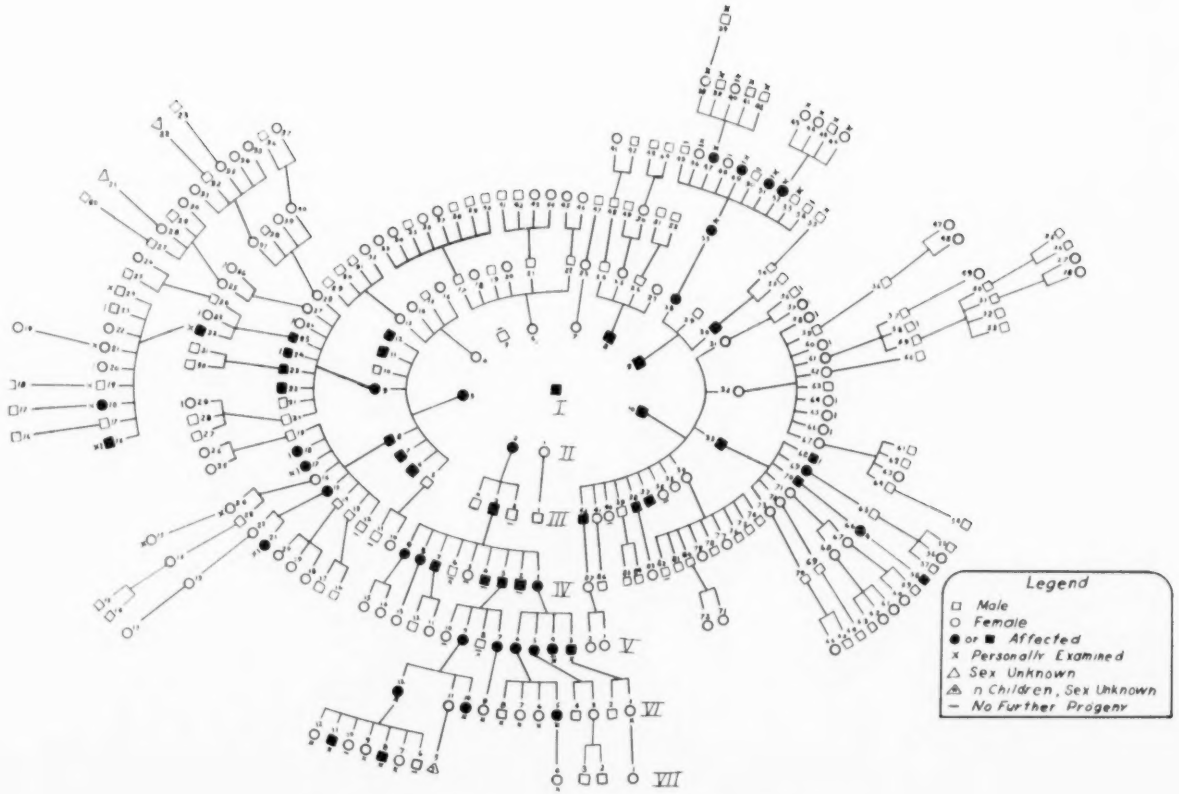

Fig. 1.—Pedigree of the L family, with peroneal muscle atrophy.

Professor Verrill was not related to this family but was a native of Norway, Maine, and a keen observer of all sorts of biological phenomena. He published in 1914 three articles in the *Oxford County Weekly Advertiser*,[31] of Norway, Maine, dealing mainly with the foot abnormality of his neighbor (*I-1*), the progenitor of this family (1770-1858), and those of his children and grandchildren. He evidently regarded this defect as a local curiosity. Professor Verrill was a paleontologist and oceanographer, but his report has considerable clinical astuteness.

For instance, he wrote of the progenitor I-1, Fig. 1: ". . . He was a most unfortunate cripple, both feet and ankles being so clubbed and turned that he had to walk entirely on his knees. Yet he was a tough old pioneer and lived to a great age, said to be nearly one hundred years, in spite of his infirmities. More than

*Comparison of Chief Clinical Data in Sixteen Cases of the L Family Examined in 1950**

			Reflexes							Muscle Atrophy							Sensory Loss						Age of Onset, Yr.	
Number	Age, Yr.	Sex	Biceps	Radial	Triceps	Abdominals	Knee Jerk	Ankle Jerk	Plantar	Peroneal	Gastrocnemius	Tibialis Anterior	Toe Flexors	Thumb Adductors	Thumb Opponents	Finger Flexors	Finger Extensors	Vibration	Position	Touch	Pain	Cold	Trophic Ulcer	Foot Deformity	Feet	Hands
V-4	57	F	0	0	0	0	0	0	0	4	4	3	4	4	4	2	0	3	3	3	4	3	+	+	3	10
V-32	58	M	1	0	0	0	0	0	0	4	3	2	2	2	4	0	0	2	2	2	3	2	+	+	5	30
V-66	61	F	0	0	0	0	0	0	F†	4	2	4	4	1	4	0	0	0	0	0	0	0	+	+	5	50
V-51	41	F	1	0	0	0	0	0	F	4	4	4	4	4	4	0	0	0	0	0	1	0	—	+	11	18
V-49	47	F	1	1	1	0	0	0	F	4	0	0	0	4	0	0	0	0	0	1	1	1	—	+	27	35
V-21	67	F	2	2	2	..	0	0	F	4	2	2	1	1	4	0	0	0	0	0	0	0	—	+	..	..
IV-17	84	F	2	0	0	0	0	0	F	4	2	1	2	1	2	0	0	1	0	0	1	0	—	+	10	40
IV-53	83	F	0	0	0	0	0	0	F	3	2	2	1	1	4	1	1	..	..	..	..	..	—	+	20	40
VI-5	39	F	..	..	..	..	..	..	..	4	2	2	..	..	..	..	..	..	..	..	..	..	—	+	10	—
VI-18	28	F	2	2	2	2	1	1	F	3	0	0	0	0	0	0	0	0	0	0	2	0	—	+	10	—
V-47	55	F	2	2	2	0	0	0	F	0	0	0	0	0	0	0	0	0	0	0	0	0	—	+	30	—
VI-10	34	F	2	2	2	2	2	2	F	0	0	0	0	0	0	0	0	0	1	0	0	0	—	+	10	—
V-3	61	M	2	2	2	2	2	2	F	2	0	0	0	0	0	0	0	1	0	0	1	0	—	+	10	30
VI-16	26	M	1	1	1	1	0	0	F	0	0	0	0	0	0	0	0	0	0	0	0	0	—	+	5	—
V-52	39	F	1	0	0	0	0	0	F	0	0	0	0	0	0	0	0	0	1	0	0	0	—	+	30	—
VI-12	43	F	2	2	2	..	2	2	F	0	0	0	0	0	0	0	0	0	0	0	0	0	—	+	—	—

* Intensity of response in the reflexes is graded 0 to 4; degree of muscular atrophy, 0 (absent) to 4 (severe), and sensory loss, 0 (absent) to 4 (severe). The case numbers refer to the pedigree (Fig. 1).
† Flexor.

twenty of his descendants inherited abnormal feet, to the fifth generation in one line." In reference to his son (*II-9*) he wrote: "Both of his feet were badly club-footed and the ankles turned in, making walking difficult. Later in life he walked mostly on his ankles."

The observations of Professor Verrill, combined with the suggestions of the amateur genealogist of the family, and information from surviving members, made possible an investigation of this extensive family, portrayed in Figure 1. This pedigree seems considerably larger than any collected by Bell[32] and shows a number of interesting features not clearly presented by previous authors.

31. Verrill, A. E.: Series of articles in a weekly newspaper, the Oxford County Advertiser, Norway, Maine, in the issues for Nov. 6, 13, 20, and 27 and Dec. 18, 1914, Vol. 45.

32. Bell, J.: On the Peroneal Type of Progressive Muscular Atrophy, in Treasury of Human Inheritance, London, Cambridge University Press, 1935, Vol. 4, Pt. 2.

The pedigree of the L family is presented in Figure 1, in which the legend explains which members are affected and which have been personally examined. In addition to the four cases to be described in detail, notes on the information available regarding the other affected members are presented in the appendix.

The clinical data on 16 members who were personally examined by one of us (A. C. E.) are presented in the table. A total of 18 affected members have been examined one or more times, some by both of us. Thirty-nine other members of the family have been described sufficiently well by others to be fairly judged as suffering from the familial disease. Thus, of 303 persons known to descend from the progenitor, 57 are affected.

TYPICAL CASE HISTORIES

CASE 1 (V-51, Fig. 1).—This woman appears to present the classic phenomena of this disease, as described by Tooth. When she was first seen in 1940, the patient, an unmarried saleswoman aged 31, complained of weakness and unsteadiness of her legs. At the age of 5 years she was found to be unsteady on her feet. This progressed to the age of 12, when she had a series of tenotomies at the Peter Bent Brigham Hospital, Boston. At this time she began to notice weakness in her hands as well as in her feet. She was unable to skate on ice and had difficulty with writing. Physicians prescribed leg-brace supports, which she did not find tolerable. She discovered that a more satisfactory foot support was obtained by a casing of adhesive plaster over both ankles. This support has been used for the past 15 years with satisfaction; it has produced only mild roughening of the underlying skin.

The patient has noted little change in the condition of her hands or feet since 1940. She has married but has refrained from having children because of her hereditary taint. The unsteadiness of gait and the weakness of her hands she considers to have increased, but only slightly. Yet she admits that she can perform everything in 1950 that she could in 1940. She has been troubled somewhat by night cramps in the muscles of her thighs and calves. These have been relieved for the most part by administration of mixed tocopherols, 50 mg. capsules, twice daily. She has taken this medication regularly since 1940.

Physical examination on April 30, 1950, revealed a well-nourished woman, then 41 years old. Her gait was fully paced but slightly stiff. When her ankle adhesive support was removed, she could barely balance herself and could not walk at all. There were considerable scaling and reddening of the skin, owing to the repeated application of adhesive plaster. The Romberg sign was not elicited. Examination of the cranial nerves disclosed that the optic disk, retinal arterioles and veins, and retina were normal in both eyes. The pupils were each 4 mm. in diameter and reacted well to light and in accommodation. The eyes moved well. Pinprick and cotton stimuli were well perceived over her face; the corneal reflexes were active. The facial muscles moved well. Her hearing, voice, throat, and tongue were not remarkable.

There was considerable atrophy of the calf muscles, resulting in a cylindrical lower leg. There was slight loss of bulk of the vastus medialis muscles. The feet were short, with high arches and toes springing upward. Her hands showed pronounced atrophy of the thenar and hypothenar eminences and of the interossei on both sides. The thumb-finger web was also thinned. These changes are illustrated in Figure 2.

As concerns muscle strength, there seemed to be about 35% of normal power of plantar flexion of the ankle, with complete absence of ability to evert the feet, flex or extend the toes, or dorsiflex the ankles. The power of flexion and extension of the knees was excellent on both sides. Hip and trunk movements were all strong. In the hands there was only a trace of ability to oppose the thumbs, while thumb adduction was vigorous on both sides. The lumbricales, interossei, and finger and wrist muscles seemed unaffected. Careful inspection of the muscles showed no fascicular or fibrillary movements.

Tests for pinprick, cotton-wool, position, and vibration (128 vibrations per second) sensation revealed only a questionable diminution of pinprick perception on the superior aspect of the toes. Tendon reflexes were absent save for a 1 + biceps reflex bilaterally. There was no response to plantar stimulation.

This patient, therefore, experienced the onset of leg atrophy in early childhood, followed several years later by wasting of the hands. Foot deformity was an early feature. The disease appears to have been more or less quiescent since the age of 30. She has now areflexia, but no fasciculation, and sensation is essentially intact.

Case 2 (V-4).—This patient has the severest case of the disease in this family group. The patient, a widow aged 57, without children, cannot recall when her feet were strong. When she was 12 years old physicians prescribed iron leg braces, and she had a good deal of difficulty in walking. She thought that weakness of the hands began at the age of 10 years. When she was 30, she became afflicted with persistent and recurrent ulcers of the right foot, for which she was studied at the Massachusetts General Hospital, at the age of 36. A neurological consultation at that time was reported on as follows: "There were weakness of grip and atrophy of the thenar eminences and of the adductors of the thumbs. The muscles of her arms were flabby and small. There was weakness of the extensors of the feet. Fibrillations were not seen. The biceps and other tendon reflexes of the arms were sluggish. The knee jerk, ankle jerk, and plantar response were absent bilaterally. The corneal and abdominal reflexes were present.

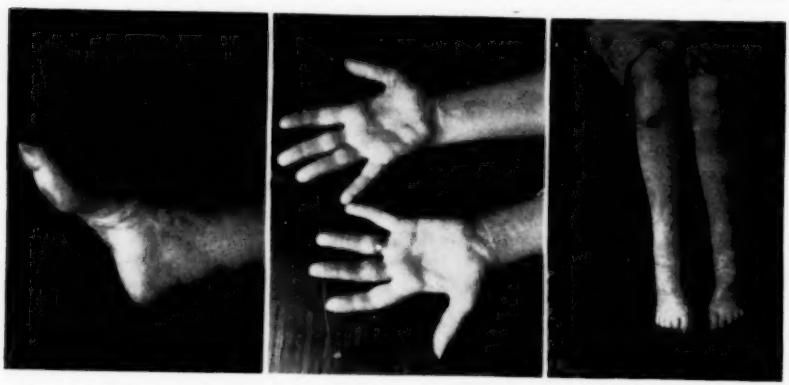

Fig. 2.—Extremities in Case 1 (V-51), showing mild pes cavus and atrophy of the opponens and adductor pollicis. There is atrophy of the lower vastus and of the calf and peroneal muscles. Marking of the skin by the customary adhesive strapping is visible.

Sensation to pinprick, cotton wool, heat, and cold was practically absent over the soles and dorsa of the feet, in the distribution of the fifth lumbar and first sacral nerves. There were diminished pinprick sensation over the anterior part of the leg in the distribution of the third and fourth lumbar nerves and less diminution over the back of the legs over the area of the second and third sacral. There was no saddle anesthesia. The sensation above the umbilicus was good." The consensus was that the condition was multiple peripheral neuritis. X-ray pictures of her ulcerated right foot showed destruction, deformity, and proliferation of the tarsal bones.

The ulceration of the foot did not respond to a lumbar sympathectomy. Later, in 1931, her right leg was removed above the knee at the Central Maine General Hospital, in Lewiston, Maine, because of persistent ulcer and osteomyelitis. She reports that since this time her left leg has become weaker. In 1938 she fell and fractured her left hip; this has healed. She has lived on one floor, using a castered stool and canes to propel herself by hand. She feels that in the past 10 years she has lost the remaining strength in her left lower leg; and that her hands have lost considerable power in ability to perform tasks involving her thumbs. In October, 1950, she was in an automobile accident and was thrown to the floor of the car. Though she had no pain, x-ray films disclosed a fracture of the left ankle. This has healed while the limb was in a light loose cast. She has never had muscle cramps.

Physical examination, April 30, 1950, disclosed a somewhat obese, alert woman, sitting on her castered stool. She had no use of her left lower leg, which hung with a swollen, bluish-white appearance and was cool to the touch. She required some assistance to lie down on the bed, but used her arms strongly in so doing. Examination of the cranial nerves showed no abnormality in the optic fundi. The pupils were round, measuring 4 mm. each, and reacted well to light and in accommodation. Extraocular motions were normal. Pinprick and cotton-wool stimuli were well perceived over her face. The facial muscles moved well. Hearing, voice, palatal reflexes, and tongue movement were excellent. The hands showed considerable atrophy of both thenar and hypothenar eminences (Fig. 3), but the only muscular weakness was inability to oppose her thumbs. She was able to hold objects in her hands well by adducting her thumb against her index finger. Finger and wrist motions were strong. There were no fasciculations. Little movement was possible below the left knee. Power of plantar flexion and of contraction of the tibialis anterior (anticus) was about 25% of normal, while the toe muscles, tibialis posterior (posticus), and peronei did not contract at all. The pale, slightly bluish swelling of the dependent leg obscured all signs of atrophy of the calves (Fig. 3). There was no certain atrophy of the vastus medialis, but power of movement of the knees was less than expected, though not weak.

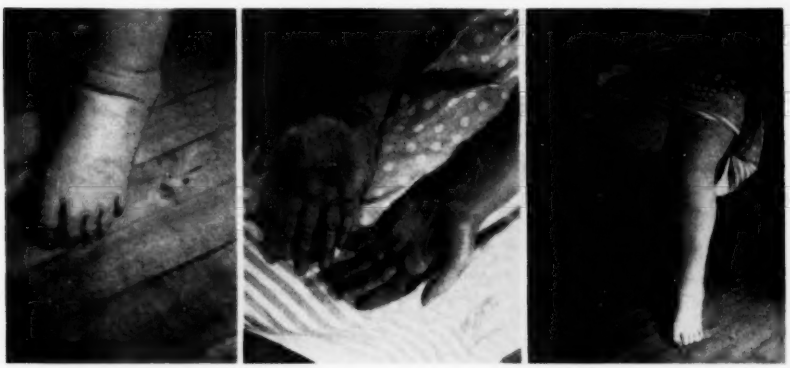

Fig. 3.—Extremities in Case 2 (V-4), showing the dependent swollen, flaccid left foot, which is short but has no cavus deformity. The hands show considerable thenar atrophy. The patient is seated on her castered stool.

On inspection, the left foot did not present the classic deformity of pes cavus. The foot was flaccid; the arch, though short, was not high. Sensory examination showed complete loss of perception of cotton-wool stimulation below the midshin level, with a fading upper border of hypesthesia above the knee, and complete loss over the hands, with a fading border above the wrists (Fig. 4). There was loss of appreciation of hot (70 C.) and cold (10 C.) stimuli over the same areas. Pinprick perception was obscured over a much wider area, extending up the trunk to the distribution of the fourth thoracic nerve, involving both arms and including all the cervical segments. The hands and feet were completely anesthetic, and there was considerable sensory diminution over the remainder of the involved region. Position and vibration sensations were poorly noted at the wrists, absent at the ankles, but preserved well on the sternum and above this level.

Tendon reflexes were absent throughout, and there were no abdominal reflexes or plantar response. Peripheral nerves were not palpated.

This woman, therefore, can be said to have had a fairly typical onset and advance of severe peroneal muscular atrophy. In contrast to the first patient (Case 1), she presents fairly general sensory involvement, as high as the first cervical segment, with trophic ulcer of the foot, necessitating amputation.

Case 3 (V-32).—This patient, a married woodsman and farmer aged 58, also presents unusual sensory changes. As a child he was not able to skate on ice and had short, high-arched feet. At 16 he began walking on the outer edges of his feet, particularly on the left side. He considered that this was because the left foot had been injured by a horse. However, both feet eventually turned in. He then realized he had the familial foot trouble, which had come down to him from his father. At 40 he felt that his hands were weak, especially in such motions as picking up pins from the floor. At 53 he had huge recurrent ulcers on the outer aspect of the left foot, where he walked. Two years ago these were especially foully infected. Finally, an amputation was done below the left knee and a prosthesis fitted to the stump. The roent-

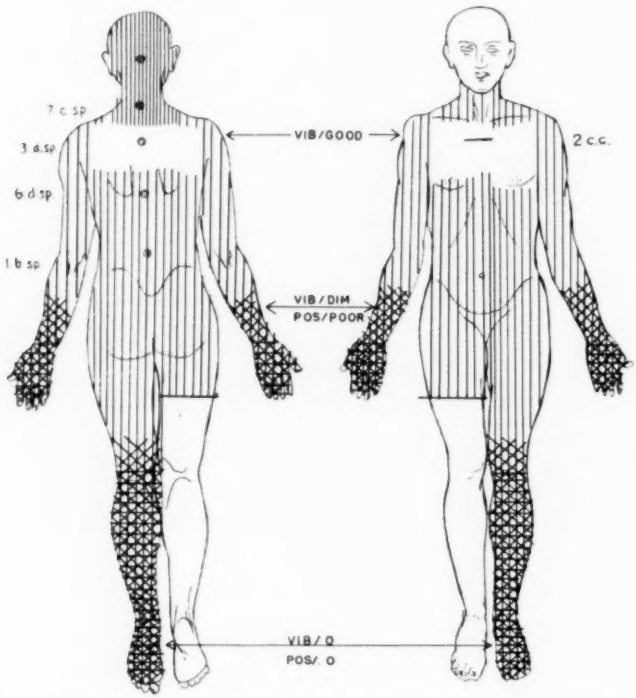

Fig. 4.—Sensory chart in Case 2 (V-4). Vertical hatching represents hypalgesia; horizontal and oblique hatching, anesthesia and loss of temperature sense, respectively.

genogram of this foot, taken in 1948, is shown in Figure 5, by courtesy of Dr. N. Louis Somers, of Dixfield, Maine.

With an artificial left foot he has managed to get around better; but the right leg has become weaker, and it is now more difficult for him to milk and to drive a team of horses. He is, therefore, about to stop farming. There has been much shrinking of the muscles below the left knee, such that his boot now fits very loosely. In July, 1950, he noticed foul sores on his right foot, and at the time of writing he is receiving aureomycin and penicillin to combat this infection.

Physical examination on April 29, 1950, revealed a weathered and somewhat bent man. The left foot was amputated above the ankle and the substance of the left calf had atrophied. The right foot was short, with a high arch, cocked-up toes, and huge, grypotic toenails. The foot was dusky red. His gait was limping but steady, and there was no Rombergism. Examination

of the cranial nerves showed that the optic fundi were within normal limits. His pupils were equal, each measuring 3 mm. in diameter, and reacted well to light and in accommodation; the extraocular movements were normal. Cotton-wool and pinprick sensibility was well felt over the face; the corneal reflexes were brisk. His face moved well; his voice and throat were

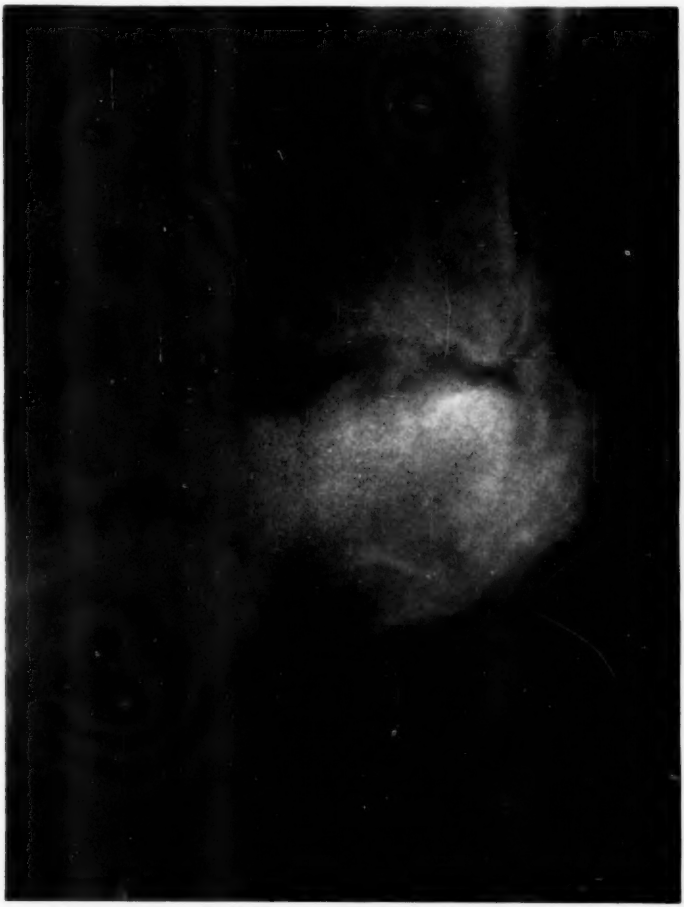

Fig. 5.—Roentgenogram of left foot in Case 3, prior to amputation in 1949, showing gross overinversion and osteomyelitis (courtesy of Dr. N. Louis Somers, of Dixfield, Maine).

normal; the palatal reflexes were active. Hearing was normal. The tongue moved well and was not atrophied.

There was atrophy of substance of the left calf, as noted. There was considerable diminution of muscular strength of the right leg muscles as follows: gastrocnemius and soleus, 25% of normal; peroneal muscles, no contraction; tibialis anterior, 50% of normal; dorsiflexors of the toes, no contraction; plantar flexors of the toes, 25% of normal. The thigh muscles, both the vastus and the hamstrings, were strong, and there was no atrophy of the vastus internus. The

hands showed considerable flattening of the thenar and hypothenar eminences. The only functional defect was in opposition of the thumb, which could not be performed. Finger and wrist motions were strong.

Pinprick and cotton-wool sensation, position sense, temperature perception, and vibration sense were diminished below the right midshin level (Fig. 6). Sensation of the hands was completely intact. The only tendon reflex obtained was a 1 + biceps reflex on each side. There was no other tendon reflex, no abdominal reflex, and no plantar reflex. No peripheral nerves were palpable.

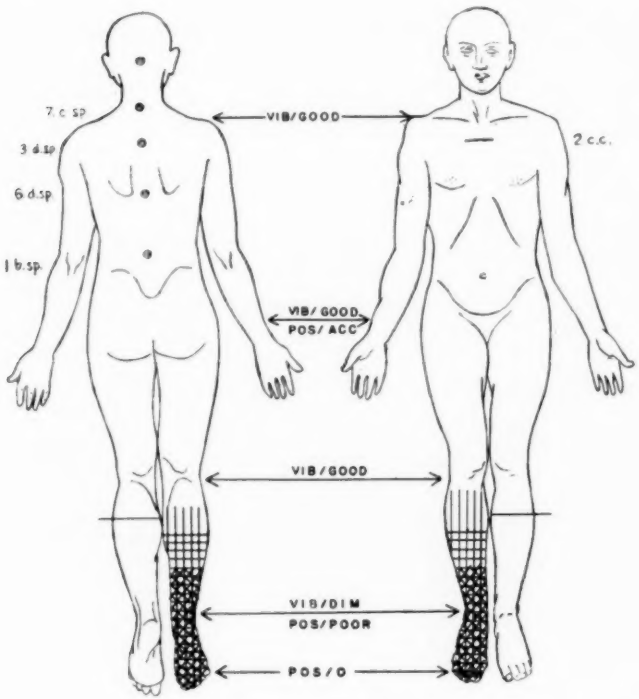

Fig. 6.—Sensory chart in Case 3 (V-32).

This man, then, had a fairly typical degree of muscular atrophy, with its onset in childhood, characterized by inverted feet with pes cavus and deformity of the toes, which is slowly progressing. Recently, serious deep, penetrating ulcers of the trophic type developed, necessitating amputation. He now finds that his other foot is threatened. Peripheral sensory loss has complicated the condition.

Case 4 (V-49).—This woman, a housewife aged 47, a sister of the patient in Case 1, presents unusually severe atrophy of the hands. She recalled that she has had unstable ankles since the age of 25. This condition has seemed to become gradually worse, and she now walks carefully to avoid turning her ankles in. She has some cramps in the calf muscles but for many years she would not admit she had a disease like that of her sister. Since the age of 25 she has had a great deal of disability with her hands. This forced her to give up typing, filing, and pen writing,

and she has been thus judged wholly disabled by her insurance company. She is not able to shuffle cards or to knit. She, too, could never learn to skate on ice. She is intentionally childless.

Physical examination, on April 30, 1950, revealed that she was a short woman of healthy appearance, with a stiff, unsteady gait and a positive Romberg sign. Her feet were short, with typical, cocked-up toes and a high arch. They seemed of normal color, without swelling, and presented good pulsation of the dorsalis pedis artery. Examination of the cranial nerves showed the optic fundi to be within normal limits. Her pupils were equal, each measuring 4 mm. in diameter, and reacted well to light. Her extraocular movements were normal. Pinprick and cotton-wool stimuli were well perceived over her face, and the corneal reflexes were normal. The face moved well. Hearing and voice were normal. The palate and palatal reflexes were active, and the tongue moved well.

The lower legs showed a cylindrical atrophy, much like that of her sister, but her muscular weakness was confined only to the peroneal groups. These had practically no function, while the tibiales and other extensors and flexors of the toes and ankles were strong. Her hands showed severe thenar and hypothenar atrophy, with some lessening of the substance of the interossei and adductor pollicis (Fig. 7). Function of the opponens pollicis was nonexistent, and her thumb was of little use, as it also could not be adducted. The long flexors and extensors of the fingers were normal, and the motions at the wrist were strong. There were no fascicular tremors.

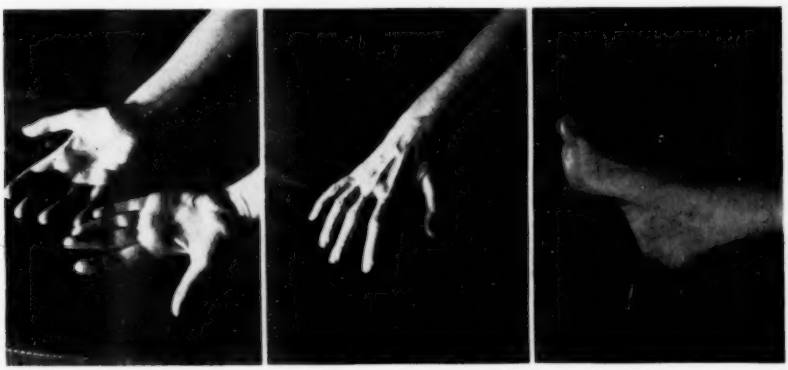

Fig. 7.—Extremities in Case 4 (V-49), showing severe atrophy of the intrinsic muscles of the hands and pes cavus.

Tests for touch (cotton wool), pain (pinprick), position, and vibration (128 vibrations per second) sensibility showed slight diminution over the dorsum of each foot; but there was no complete loss. She had good tendon reflexes in her arms, but no knee or ankle jerk and no plantar reflex.

This patient, then, demonstrates that the same inheritance of peroneal muscular atrophy which caused extensive atrophic disease in her sister had led in her case to atrophy in the peroneal muscles only. However, the atrophy affected her hands to a greater degree. The reflex disturbances were less widespread, and the sensory changes were slight in degree.

COMMENT

This familial disease is clearly a form of the peroneal muscular atrophy of Charcot and Marie, and Tooth. Of 303 persons known to descend from the progenitor of this large family, 57 are known to be affected. Of these, only 18 have been personally examined, but the evidence collected by Professor Verrill in

1914 has been corroborated at many points by elderly members of the family still living, for example IV-6, who recalls his grandfather well, and many other relatives. There was no discovered instance of a person falsely considered to suffer from the disease. As might be expected, there is a psychologic tendency wishfully to be free of the taint. Two severely afflicted branches, namely, that of the family of III-3 and that of the family of III-28, humorously each called the disease by the name of the other branch, as the C disease and the L disease, respectively!

The inheritance of the disease has been exhaustively analyzed by Bell,[32] who found no essential difference in the dominant, recessive, and sex-linked types. The contention of Allan [33] that recessive inheritance was usually the earliest in onset, the severest and the most crippling, has not been borne out by Bell's analysis or by the distribution in the L family. The distribution of affected members in our family is 31 males and 26 females, showing no sex predilection, in agreement with the findings of Bell.[32] In no instance was an afflicted person found without a parent's being similarly affected. A seven-generation passage has been defined, as illustrated by I-1, II-2, III-3, IV-3, V-9, V-12, and VII-8. In any one family of siblings, it is usually a minority that displays this syndrome. The 9 children of III-9 showed 4 moderately affected members; the 10 children of IV-53, 4 affected members. The original I-1 had 10 children, of whom 5 had the disease. The pedigree chart (Fig. 1) shows that only rarely is the "penetrance" (an approximation to the predicted 50% affected cases of purely dominant genes) complete. In the case of I-1 it appears to be so. The existence of the disease in seven of nine offspring of III-3 would be an error unless the wife of this patient also carried the disease. The existence of an isolated deformity of the feet in the sisters V-10 and V-12 indicates that small feet with cocked-up (hammer) toes may be a minimal expression of the condition.

There seems to be a genetic tendency of the syndrome to disappear, for as the family increased there were more members of the family who were unaffected themselves and siring unaffected lines of progeny than affected ones siring affected lines. The statements of members of the unaffected family of the allegedly afflicted II-8 appear to illustrate this. However, it cannot be conclusively established that II-8 himself really presented the condition.

Voluntary refusal to procreate is very common in contemporary generations, and it was admitted to us several times. Bell [32] wrote of similar admissions. The disease does not affect procreativity in any way, nor does it affect length of life.

Some authors have believed that their pedigrees of peroneal muscular atrophy demonstrated the phenomenon of anticipation, or progressively earlier onset of the disease in descending generations. Schwartz's [34] family has been cited as evidence of such anticipation in 123 members in five generations, of which 23 were affected. The family we have described does not have any indication of anticipation. The usual age of onset of the first symptom is 5 to 10 years in severe cases

33. Allan, W.: Relation of Hereditary Pattern to Clinical Severity as Illustrated by Peroneal Atrophy, Arch. Int. Med. **63**:1123 (June) 1939.

34. Schwartz, L. A.: Clinical Histopathological and Inheritance Factors in Peroneal Muscular Atrophy (Charcot-Marie-Tooth Type), J. Michigan M. Soc. **43**:219, 1944.

and 10 to 25 in milder ones, and has been as late as 50, but the disease then is minimal. Examples of all three degrees are scattered at random in the generations.

Peroneal muscular atrophy in this particular strain, then, is a hereditarily determined appearance of flaccid atrophic paralysis of the peroneal muscles, with a variable degree of a similar affection of other muscles of the legs and of the hands. It appears often in childhood but in rare instances may occur up to the age of 50. The earlier its appearance, the more serious will be the ultimate disability.

In a consistent fashion, severe involvement has been presaged by the development in childhood of a short, wide, extremely high-arched foot. The toes appear to spring upward and then to curl sharply down. This is the characteristic pes cavus of the disease and differs in no way from the deformity of the foot associated with Friedreich's ataxia. The term "clubfoot," used for this deformity by lay writers, is a misnomer. The evidence suggests that when weakness of peroneal and ankle extensor muscles develops in childhood the growing bones are molded by the muscle tensions. We have no evidence as to the part played by the changes in the intrinsic muscles of the foot. The feet in Case 2 show that in the complete absence of muscular power in the foot the cavus deformity may tend to flatten out or not to develop, leaving a flaccid, flat foot.

In each afflicted member of this pedigree, the peroneal muscles were always the most severely affected. Usually the tibialis anterior was almost as atrophic. Further spread involved the plantar flexors of the foot and toes, but usually these muscles still showed traces of movement in the worst sufferers. Muscular atrophy was often almost complete below the knee; yet the patients could walk well by virtue of constant practice, aided by ankle fusion or adhesive-plaster support of the ankles, and efficient use of the remaining musculature.

In the hand, the usual involvement was of the opponens pollicis, which was often completely atrophic. The second and third interossei were often involved, and in two cases, the adductor pollicis was affected. There were no instances of weakness of the forearm, though slender flexor muscles were seen. Fasciculation was not observed.

Absence of tendon reflexes is a very common occurrence. Only 4 of 16 persons seen had ankle or knee jerks, and these had the 4 mildest instances of the disease (Table). Complete absence of tendon reflexes, even in the upper limbs, occurred in three persons. The tendon reflexes were often lost in muscles which showed neither atrophy nor weakness. As in other forms of peripheral neuropathy, the tendon reflexes appear to be especially sensitive.

Extensor plantar responses were not seen. There was no hypertrophy in any peripheral nerve. The pupils were equal and reacted well to light in each instance. In this family there was no appearance of Friedreich's ataxia, spastic paraplegia, or optic atrophy.

The family is particularly remarkable for the degree of disorder of sensation which developed in some members. In Cases 2 and 3 anesthesia in the feet had led to perforating ulcers and osteomyelitis, necessitating amputation. In others the sensory changes were minimal in degree. Severe loss of sensation appeared when the disease had been early in onset and severe in degree. This had occurred independently in three family groups in the fifth generation and could, therefore,

not be due to a mutation in the disease. The changes found by Charcot and Marie in their nonfamilial case "Sultz," in which Marinesco[6] subsequently performed autopsy, may therefore be accepted as typical. Raymond[30] also described a family with severe sensory changes, but the presence of thickened nerves would appear to indicate that the condition was the chronic interstitial hypertrophic neuritis of Dejerine and Sottas. In our own cases there was no evidence of thickened nerves. The pattern of the sensory loss, its wider extent to touch than to pain, and its first appearance over the outer border of the foot and leg indicate a radicular distribution, with approximately the same severe incidence in the fifth lumbar nerve roots that is indicated by the onset and severity of motor peroneal atrophy. The occurrence of such sensory loss and its pattern indicate that the disease is essentially a radicular neuropathy, and not a disease of the spinal cord.

Though no pathological verification of the disease process in the L family has been possible, we would revive the view originally expressed by Tooth, namely, that peroneal muscular atrophy is a hereditary disease of the peripheral nervous system, substituting the term "hereditary radicular neuropathy" for Hoffmann's "neurotic atrophy." The pathological findings of Virchow and Marinesco appear typical of the severe form of the disease. The findings of others, cited in the introduction, of some degeneration in the dorsal columns of the spinal cord in cases in which sensory changes had been minimal, or not apparent, is not necessarily an indication that such degeneration is primarily a spinal process, as Marinesco and Sainton proposed. It has a more obvious explanation in that perhaps only one sensory root was severely affected, with resulting difficulty in clinical detection, owing to an overlap of supply of neighboring nerve roots.

The family described here, as with a number of other large families with peroneal muscular atrophy, gives no evidence of ataxic variants of the disease, or of a common type of areflexia with pes cavus, giving rise to atrophic palsy in some members and Friedreich's ataxia in others. Such families as are reported by Roussy and Lévy,[19] Rombold and Riley,[21] Ross,[18] Spillane,[24] and others appear to us to be suffering from a separate condition, running a different course even in their atrophic types, and therefore requiring a pathology other than that of classic peroneal muscular atrophy. Thus, it is common for all the tendon reflexes to be absent, even in minimal development of the Roussy-Lévy syndrome; dysarthria and scoliosis also are present in minimal cases, and Roth[35] noted eversion of the foot. The atrophy affects the trunk musculature in severe cases (Roth), and mental disorder is common. We have recently had a case from such a family under observation in which all these features were exhibited. It was especially noteworthy that the peroneal muscles still contracted and were not more severely weakened than the other muscles below the knees. The feet, though deformed, were not inverted. Dysarthria was prominent, but there was no nystagmus.

When it is considered that chronic interstitial hypertrophic neuritis has already been sharply separated from the Charcot-Marie-Tooth peroneal atrophy, it is clearly possible that yet other variants of familial atrophic paralysis may ultimately be differentiated from the general group of familial amyotrophies. Van

35. Roth, M.: On a Possible Relationship Between Hereditary Ataxia and Peroneal Muscular Atrophy, with a Critical Review of the Problems of "Intermediate Forms" in the Degenerative Disorders of the Central Nervous System, Brain **71**:416, 1948.

Bogaert [36] has recently stressed the finding of unsuspected spinocerebellar degeneration in cases of progressive familial amyotrophy occurring in childhood when cerebellar symptoms had not been manifest in life. Such cases, and those described by Gierlich,[11] should be set aside as representing a separate entity of the familial spinal amyotrophies, to which the Roussy-Lévy syndrome also appears to belong.

In the L family with peroneal muscular atrophy described here, minimal variants of the disease were distinguished by late onset; short, broad feet with weakness of eversion; pes cavus with inversion; absence or feebleness of the ankle jerk, but often with preserved knee jerk, and sometimes great weakness of adduction of the thumb. These features also distinguished the families described by Symonds and Shaw,[29] in which dysarthria was absent, and appear to constitute a true forme fruste of Charcot-Marie-Tooth atrophy. The condition does not bear more than a superficial resemblance to the syndrome described by Roussy and Lévy. Minor variants of peroneal muscular atrophy may be expected to occur, and differing degrees of sensory involvement are clearly part of the true syndrome. It is possible that the variety of the disease which presents coarse fasciculation of the muscles, recognized since Tooth's description, is also different from the better known syndrome, in which fasciculation may be sought in vain. The hereditary disease described by Hicks [37] as "hereditary perforating ulcer of the foot," and shown recently by Denny-Brown [38] to be a peripheral neuropathy, may more properly be included as a variant of peroneal atrophy, for its clinical manifestations indicate only a different accentuation of the radicular disease resulting in preponderance of sensory degeneration. All these conditions should be grouped as radicular neuropathy, in our opinion.

SUMMARY

A large family with a dominant inherited trait of peroneal muscular atrophy (Charcot-Marie-Tooth syndrome) is described, consisting of 303 members directly descended from one affected male, in seven generations.

Data regarding 57 affected members are presented. Of these 57 members, 18 were personally examined.

Two patients presented extensive sensory and trophic changes, of a type consistent with a radicular neuropathy, in addition to the classic syndrome. This was the severest type of the disease.

Cases of the mild, forme fruste, type are described, in which slight pes cavus was present, without tendon reflexes necessarily having been lost.

The age of onset was 5 to 10 years in severe cases, and 10 to 25 in cases of the moderately developed form, and has been as late as 50, in which the disease then presented a mild, arrested type. Examples of all three degrees of severity are scattered at random throughout the pedigree.

The relation of the condition to the degenerative diseases of the spinal cord is discussed, and it is concluded that true peroneal muscular atrophy should be distinguished sharply from the Roussy-Lévy syndrome.

36. van Bogaert, L.: Sur les formes d'hérédoataxie de l'enfant et de l'adolescent qui comportent une atteinte grave des noyaux moteurs spino-bulbo-mésencéphaliques, Rev. neurol. **84**:121, 1951.

37. Hicks, E. P.: Hereditary Perforating Ulcer of the Foot, Lancet **1**:319, 1922.

38. Denny-Brown, D.: Familial Radicular Sensory Neuropathy, J. Neurol., Neurosurg. & Psychiat., to be published.

APPENDIX

Clinical data concerning the affected members shown in Figure 1 follow:

I-1: See quotation from Verrill in the text. He also wrote, ". . . L. was obliged to walk on his knees, owing to this defect, which he had in extreme form, in both feet and ankles."

II-2: Verrill wrote, "I think that all of his [D.'s] children had clubbed feet, more or less marked. . . . She was a daughter of D. and had clubbed feet."

II-3: Verrill wrote, "Her feet were badly deformed."

II-8: Verrill wrote, "P., mentioned above, had his feet less deformed than most of the others."

II-9: See text.

II-10: An acquaintance who has known the family for many years informs us that his feet were "really bad." V-71 said, "He had the 'pumple' foot, but his hands were all right." ("Pumple foot" is the name given this condition by many of the family. Its origin is obscure.)

III-3: Verrill wrote, "He was a congenital cripple, having both feet badly clubbed, an unfortunate inheritance from his maternal grandfather, L."

III-6: Verrill wrote, "He wore boots which were small and of unusual shape."

III-7: Verrill wrote, "His feet were small." V-24 said she did not believe he had the disease. However, IV-17 said, "His feet weren't perfect, but he could get around."

III-8: IV-17, his daughter, aged 84, said he had the "pumpled" feet. IV-26 wrote that her uncle had clubfoot, high insteps, and hardly any toes.

III-9: V-24 thought that she had the "bad feet." There is no more definite word about her.

III-11: Verrill wrote, "His walk was abnormal."

III-12: Verrill wrote, "He had abnormal feet."

III-28: Verrill wrote, "E. apparently had normal feet but an odd gait."

III-30: Verrill wrote, "A. was badly club-footed, but less so than his father."

III-33: V-71 said, "He had pumple feet, just a good twisted foot, a big hump. He had his shoes made. His hands were all right."

III-37: V-71 said, "He had the pumple feet."

III-38: V-71 said, "He had the bad feet, the usual stumps."

III-42: V-71 was sure he had bad feet.

IV-1: Verrill wrote, "She had more or less abnormal or crooked feet." V-4 thinks her mother was affected but cannot recall details, as she was not reared by her mother.

IV-2: Verrill wrote, "His feet were abnormal."

IV-3: Verrill wrote, "His feet were abnormal." V-4 said his feet were affected, but not badly. An informant who has known the family for many years informs us that he had "pumpled, tiny feet."

IV-4: Verrill wrote that his feet were abnormal.

IV-7: IV-6 said he had bad feet.

IV-8: IV-6 said she had bad feet.

IV-9: IV-6 said she had bad feet.

IV-15: V-21 said, "She was on crutches the last years of her life and always wore special shoes. However, her hands were not affected." But IV-17, her sister, said she was "The worst case in the family."

IV-17: This person, an elderly single woman of 84, said she had always had a high instep. Her ankles had become somewhat swollen of recent years. She never skated very much, but had been on ice skates, abandoning them because she had weak ankles. She denied any difficulty with her hands.

Physical examination, on April 30, 1950, disclosed a feeble and mentally limited woman, with an unsteady gait and a Romberg sign. Her cranial nerves were within the limits of normal. Examination of her feet disclosed that her toes were blue and edematous. There was some loss of muscle substance in the calf. Muscle testing showed complete absence of peroneal muscles and the extensors of the foot and about 25% of normal power in the tibialis anterior. The hands

showed thinned thenar eminences, and the left opponens pollicis was weak. The rest of the muscles were strong. Sensory examination showed hypesthesia to pinprick below the ankle and diminution of vibration sense (128 vibrations per second) at the ankle. There were no other sensory abnormalities. Knee and ankle jerks were absent, but the biceps, radioperiosteal, and triceps were graded 1+. There was a flexor plantar response.

She seems to have had a mild affliction, rather stable for many years, with some disability, and to have the complications of arteriosclerosis and senility.

IV-18: A detailed account of this woman's disease was given by her brother, IV-19. He remembered that she could walk when she first went to school, at the age of 6. A year later she had difficulty, with falling, and had to pull herself up with her hands. A few years later she was using a wheel chair and might at times stand briefly on her feet. From this time she remained an invalid, never married, and succumbed at the age of 40 to intercurrent disease.

IV-22: V-24 believed that he was affected.

IV-23: V-24 believed that he had bad feet.

IV-24: V-32 said his uncle had very bad feet, and always had his shoes made to order. V-24 agreed he had bad feet.

IV-25: V-32 thought he had bad feet but had no close association with him, being raised by another relative. V-24 thought his feet were affected.

IV-53: This woman died in 1950, at the age of 83, having been married four times and having borne 10 children! When seen in 1940, she would not admit that there was anything wrong with her feet or hands. Physical examination revealed a rather feeble elderly woman. The cranial nerves were not remarkable. There were about 50% of normal peroneal strength and some weakness of the extensors of the foot; the rest of the foot muscles were strong. Her hands were flat, with marked wasting of the thenar and hypothenar eminences, and the thumbs could not be opposed. Sensibility to pinprick and cotton stimulation was normal, as was position sense. Her feet were short and high-arched.

This patient is an example of moderate motor disability of the feet and hands without sensory changes.

IV-68: V-71 said his feet were very bad; he was a cripple and had never married. V-66 confirmed this.

IV-69: V-71 said he had the "pumple" feet.

IV-70: His daughter, V-66, said that he had the family feet, but "not a bad case" (i. e., he was not confined to a wheel chair!).

V-3: This member, dairyman and farmer aged 69, says he has had peculiar feet as long as he can recall. Since the age of 30 he has noted that his hands are less useful and stiffen a good deal in cold weather, making milking difficult. As a child he could skate on ice, but did so very poorly.

Physical examination, on April 30, 1950, disclosed a well-developed, weather-beaten man. There was no disorder in the cranial nerves. Examination of the muscles of the hands and feet showed nothing abnormal. Sensibility for vibration (128 vibrations per second) and pinprick were slightly diminished on the dorsa of the feet. His feet were very short with a high arch and seemed blue and cool.

This man's state seems to constitute a minimal, dubious example of the disease.

V-4: This patient is Case 2 of the text.

V-5: Verrill wrote that she had deformed or somewhat abnormal feet. V-24 said she was affected. V-4 said she had poor feet and poor balance.

V-6: Verrill said her feet were abnormal. V-4 said both her hands and feet were affected.

V-7: A friend of the family who has known them for many years reports that V-7 had poor feet, to her personal knowledge.

V-9: A friend of the family thinks this woman's feet were affected. She was never known to her daughters, and was out of touch with her family for a long time.

V-21: This patient, vigorous, twice-divorced woman aged 67, had never had children because of her inherited disease. She said she had had bad feet in childhood and had many tendon transplants by prominent Boston orthopedic surgeons, at the ages of 11 and 12. She thought she

walked normally at first, but could not skate on ice, and soon she limped and had to have custom-made shoes. She could get around on her feet, but they seemed to have "no endurance." Since the age of 55 she had to use a cane or a crutch all the time. Recently her feet were numb on arising; this also affected her hands. Her last letter said that she now felt "completely well," having benefited from evangelical teachings.

Physical examination, on May 11, 1946, disclosed an alert woman for her age, clearly an advanced cripple, who hobbled about on two stout canes. Her pupils were equal, and reacted well to light and in accommodation. The optic fundi were normal; her face moved well; hearing was normal, and her tongue moved well in the midline. She presented very short and extremely high-arched feet, about 5 in. (12.6 cm.) long and 3 in. (7.5 cm.) wide, with many calluses, which seemed to have come from wearing badly fitting shoes. The peroneal muscles had no power, and the foot extensors were weak, but the foot flexors seemed strong. There were flattening of the thenar and hypothenar eminences and hollowing to some degree in the interosseous spaces of the hand. The opposition of the thumb was weak. Vibration and pinprick sensations both were normal. Knee and ankle jerks were absent.

This case appears to be an instance of moderate motor disability of the hands and feet, beginning in childhood and advancing very gradually in adult life, without sensory changes.

V-32: His case is described in the text.

V-47: This patient, a housewife aged 39, whose sisters have been described in the text, states that she was thought to have had "infantile paralysis" at the age of 3 years. She could not skate on ice. For the past two years she feels she has had some weakness of the left forearm. She has arm and leg cramps, but these are relieved by use of tocopherols, 50 mg., twice a day. Her feet have always been short.

Physical examination, on April 30, 1950, revealed a well-preserved woman of her age. Gait and stance were normal. The cranial nerves seemed within normal limits. Examination disclosed that her feet were short with high arches and dorsally curled-up toes, in the usual manner of patients with pes cavus. There was no atrophy of the calf, foot, or hand, and the muscles tested were all strong. Pinprick, vibration (128 vibrations per second), cotton, and cold sensibility were all excellent. Position sense was slightly diminished at her toes. Knee jerks, ankle jerks, plantar reflexes, and radioperiosteal reflexes all were absent. Biceps and triceps reflexes were graded 1+.

This case represents very mild involvement, with pes cavus, cramps, no muscular weakness, some areflexia, and slight sensory change, coming on at the age of 39.

V-49: Her case is described in the text.

V-51: Her case is described in the text.

V-52: This patient, a housewife aged 55, the oldest of the four affected sisters mentioned above, reported that she had had weak feet for the past 20 years, that she wore arch supports, and that many foot calluses had developed. She did not think her hands were affected. As a child, she was not able to skate on ice.

Physical examination, on Jan. 2, 1950, revealed a healthy woman of somewhat stout proportions. Gait was normal, and the Romberg sign was not elicited. The cranial nerves were not remarkable. Her feet were short with a moderately high arch. Her hands showed thenar and hypothenar atrophy. Muscle examination showed no diminution of power in the hands and 25% of normal peroneal strength in the feet. The remainder of the foot musculature was normal. Biceps, triceps, and radioperiosteal reflexes were 2+, but knee and ankle jerks could not be obtained. The plantar reflexes were absent. Sensory examination showed that perception of pinprick and vibration (128 vibrations per second) was well preserved.

This seems a definite, though minimal, example of the condition, in a person who would not admit herself that she had it. She has peroneal weakness, short feet, atrophy in the hands, and areflexia in the legs.

V-66: A widow aged 61, a housekeeper, states that at the age of 6 years she was brought to an orthopedic surgeon, who operated on her feet. After this her feet "seemed to grow no more." Her balance became weaker, so that her parents forbade her such childhood games as skipping rope. She thinks that her "heel cords" were lengthened and her feet straightened by this surgeon. Her family believed that she had "clubbed feet," but admitted that it was a hereditary

phenomenon in her case. At the age of 10, after a fall, her hands became progressively weaker; and after a few years she abandoned the piano on which she had previously acquired some skill. She states that in 1949 she had a long siege of toe infection, due to ingrown nails.

Physical examination, on Aug. 5, 1950, disclosed a small woman with a markedly teetering gait and a Romberg sign. Her shoes were extremely small and broad (size 1½ EE) and did not fit well; her feet were very short and very wide. The arch itself was not raised. The cranial nerves were not remarkable. The hands showed pronounced atrophy of both thenar and hypothenar eminences and of the interossei. There was slight hollowing of the flexors of the right forearm. The calf muscles were somewhat atrophic, but the pretibial muscles were firm, with no detectable loss of bulk by palpation. There was, however, slight loss of substance of the mesial lower aspect of the vastus internus muscles.

In the hands, tests showed that the opponens pollicis was almost completely nonfunctional. The adductor pollicis was strong bilaterally, as were the other muscles of the hand and forearm. At the ankle, the only muscle power was ankle flexion, which was 25% of normal. Motor power at the knees was normal.

The sensation of touch was diminished from the middle of the leg downward on the right side and over the left foot, but was not lost in any part. Sensation to pinprick was blunted over the whole right leg to just above the knee and over the left leg to just below the knee. There was also some hypalgesia over the terminal phalanges of the fingers of both hands. The sense of position was absent in the toes of the right foot and present, but poor, in those of the left foot. Vibration sense was unaffected.

This case presents a syndrome of classic peroneal muscular atrophy, with mild sensory changes. It must be that constant practice makes it possible for the patient to retain the ability to walk. The strength of the lower legs is seriously diminished.

VI-5: A housewife aged 39 stated that she was very unwilling to undergo any examination and that she knew nothing of hereditary bad feet. Her foot trouble was said to be due to "an operation on her left hip as a baby." However, other members of her immediate family, especially her aunt, V-4, said she was "like all the rest."

Physical examination, on April 30, 1950, was incomplete, but she was observed to have short and grossly misshaped feet, and she hobbled along with much difficulty. She apparently also had foot drop and dragged her toes on the sidewalk.

This woman has a fairly severe form of peroneal atrophy and pes cavus.

VI-10: A housewife aged 34, childless, said that she was never able to skate on ice properly, even with ankle supports. She knew she had very short feet and that she could not stand on them without pain for any protracted period. However, she did not believe she had the family trait.

Physical examination, on April 30, 1950, showed nothing save very short (children's size 11) feet, about 11 cm. long. Her arch was short, and the toes seemed to rise upward. The sensory, motor, and reflex systems were normal.

This case is an instance of pes cavus without any other stigma. It seems only a dubious example of the condition.

VI-12: A housewife aged 40, a sister of VI-10, had never considered herself ill in any way and knew nothing of her heredity. She had lost contact with her family. She admitted that her feet were like those of her sister, exceedingly small. She, too, wore children's shoes.

Physical examination, on April 30, 1950, showed that the cranial nerves, musculature, and sensory and reflex systems were intact. Her feet, however, were, indeed, much like those of her sister, with more breadth than normal, and high, cocked-up toes. They were normal in color.

She, too, must be considered as having a minimal form of this syndrome.

VI-16: A farmer aged 20, single, thought that his feet had always been somewhat weak. However, he could skate on ice. His feet never were as strong as those of his friends.

Physical examination, on April 29, 1950, disclosed a normal-appearing young man with steady gait and absence of the Romberg sign. The cranial nerves seemed within the limits of normal. His feet were slightly high-arched and short. The musculature was intact, as was sensation. The tendon reflexes of the arms were graded 1+. The knee and ankle jerks were absent; the plantar reflexes were flexor.

This young man has some subjective weakness of the feet, areflexia of the feet and slight pes cavus and is considered to have a minimal form of the disorder.

VI-18: A housewife aged 26, says she has always had weak ankles, but perfectly strong hands. She did not skate on ice and could never run.

Physical examination, on Jan. 1, 1950, disclosed that she was apparently well. Gait and stance were normal, and Romberg's sign was not elicited. Examination of the cranial nerves revealed nothing remarkable. Her feet were high-arched but otherwise normal. There was no muscular atrophy or fibrillation. The strength of the peroneal muscles seemed to be about 25% of normal. No other muscle of the foot or hand was affected. Cotton-wool, position, and vibration (128 vibrations per second) stimuli were alike well felt. Perception of pinprick was diminished to some degree below the knee. Tendon reflexes, 1+, were present throughout, and the plantar response was flexor.

This woman seems to have weakness of the peroneal muscle, slight pes cavus, and a slight sensory disturbance.

VI-58: An accountant aged 36 is described by his afflicted mother, V-66, as having worse feet than she. Since she has fairly severe motor weakness of the hands and feet, this means he has already pronounced disability. He is said to walk peculiarly, and to have deformed feet and trouble with his hands. This man will not permit an examination.

VII-8: Of this schoolboy aged 16, his mother, VI-12, said that his feet were never right, that he wore 6½ EE shoes, and that he fell and hurt his back two years ago. She added that he was in a plaster body spica for a year. He was seen by one of us (A. C. E.) to have short feet, a cavus deformity, and a peculiar walk. A complete examination was not allowed. He is considered to present a mild form of the disease.

VII-11: This boy, aged 7 years, had a much deformed left foot, and a right foot which was less so, according to his mother, VI-12. Physical examination was not permitted, though from a distance his feet were seen to be misshapen. He is considered to be affected by the disease.

DYNAMIC CONCEPTS OF MIGRAINE

A Character Study of One Hundred Patients

A. R. FURMANSKI, M.D.
VAN NUYS, CALIF.

THE EARLY papers on migraine well recognized the psychical manifestations in the migraine syndrome, but these were considered to be primarily prodromes or effects of the actual attack, being secondary to the vascular storm.[1] A few patients were considered to have neurotic tendencies in the general personality structure. Moersch [1a] noted that the migrainous make-up tended to predispose to hysterical disturbances and remarked on its increased susceptibility to depressions at the menopause. But on the whole the formulation that the migrainous person was emotionally and psychologically normal between attacks was widely accepted. When the life histories of migrainous persons were more extensively analyzed, it became more and more evident that the personality structure in migraine played a fundamental etiological role.

Touraine and Draper [2] concluded from their study that migraine was a syndrome comparable to any other neurosis, occurring in a person of special constitutional type, produced by conflict between the desire to escape from the influence of the mother and a compulsion not to leave her. Knopf,[3] in a study of 30 patients, observed that most of the patients had histories similar to those found in cases of psychoneurosis and personal maladjustment, especially the latter. She concluded that situational stresses reacting on a special migrainous constitution resulted in the migraine syndrome becoming manifest. Trowbridge and associates [4] studied 16 patients and gained the impression that the migraine patient was similar to the psychoneurotic patient as far as personality make-up was concerned. Slight,[5] in a study of 50 patients, found that often the conflicts were deep-seated and of long standing and involved not only situational difficulties but a disturbance of the whole attitude.

From the Ross Loos Medical Group, Los Angeles.

Presented at a meeting of the Los Angeles Society of Neurology and Psychiatry on April 18, 1951.

1. (*a*) Moersch, F. P.: Psychic Manifestations in Migraine, Am. J. Psychol. **3**:697 (April) 1924. (*b*) Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429, 1932.

2. Touraine, G. A., and Draper, G.: The Migrainous Patient, J. Nerv. & Ment. Dis. **80**:1 (July) 1934; **80**:183 (Aug.) 1934.

3. Knopf, O.: Preliminary Report on Personality Studies in 30 Migraine Patients, J. Nerv. & Ment. Dis. **82**:270 (Sept.) 1935.

4. Trowbridge, L. S.; Cushman, D.; Geneva, G. M., and Moore, M.: Notes on the Personality of Patients with Migraine, J. Nerv. & Ment. Dis. **97**:509 (May) 1943.

5. Slight, D.: Migraine, Canad. M. A. J. **35**:268 (Sept.) 1936.

Wolff,[6] in his comprehensive monograph, reported his study of 46 patients and concluded:

> In short, certain individuals have a predisposition and psychobiologic equipment which makes them prone to sustained and pernicious emotional states. During such states, labile physiologic mechanisms set off the chain of events constituting the attack of migraine.

One of the important contributions to the psychogenesis of migraine was Fromm-Reichmann's[7] report of eight patients whom she had psychoanalyzed. She observed that all her patients suffered from unresolved ambivalence, that they were unable to be aware of hostility against beloved persons and tried to repress this hostility. The fundamental reason for the repression of hostility in her cases was the fear of punishment by being deprived of the family's approval and protection. She considered migraine a physical expression of unconscious hostility against consciously beloved persons. The patients, she felt, had introjected their beloved, but also hated, persons so that when they punished themselves they at the same time were injuring the introjected persons.

Psychoanalysis has opened a new approach to the study of character patterns. Freud,[8] Abraham,[9] and Jones[10] have laid the firm foundations of psychoanalytic characterology. Character, defined as a habitual manner in which the ego adjusts to the demands of the instinctual self, the critical self, and society,[11] can be observed much more easily than the unconscious. The group of character traits possessed by the individual represents a longitudinal summary of its successes and failures in the development of its instinctual life in our society. Using the dynamic mechanisms evolved from psychoanalytic research, one can obtain workable data from the pattern of the defenses as to what the underlying conflicts and frustrations are, as well as the sources of gratifications. Knowing the assets and debits of the ego, one can attempt to restore emotional balance more skilfully.

Whether the character traits signify sublimations of instinctual forces or reactions to conflictual emotions is of particular importance. The importance of this differentiation is that the sublimations channelize the instinctual stream and are of great asset to the individual. Reactive traits, on the other hand, avoid or oppose the prohibited emotions through a rigid and cramped system of defenses, resulting in fatigue and inflexibility and decrease in effectiveness. Periodically the repressed impulses break through in actions or dreams and further disturb the emotional life of the individual. The transformation of disturbing reactive traits into genuine ones of the sublimation type is one of the chief goals of psychotherapy.[11]

The various character patterns in migraine have been well described and their presence consistently reported by various investigators.[12] Much of the therapy,

6. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948, p. 348.

7. Fromm-Reichmann, F.: Contribution to the Psychogenesis of Migraine, Psychol. Rev. **24**:26 (Jan.) 1937.

8. Freud, S.: Collected Papers, London, Hogarth Press, Ltd., 1924, Vol. 2, pp. 45 and 164.

9. Abraham, K.: Selected Papers, London, Hogarth Press, Ltd., 1942, Chaps. 23-26.

10. Jones, E.: Papers on Psychoanalysis, Ed. 3, Baltimore, Williams & Wilkins Company, 1949, Chap. 24.

11. Fenichel, O.: Psychoanalytic Theory of Neurosis, New York, W. W. Norton & Company, Inc., 1945, Chap. 20.

12. Touraine and Draper.[2] Knopf.[3] Trowbridge and others.[4] Slight.[5] Wolff.[6] Fromm-Reichmann.[7]

however, has been directed primarily toward adjusting the patient's overt character traits, rather than working with the basic emotions that underly such character traits. For example, a reactive trait interpreted as it appears on face value would lead the therapist astray, since the basic emotion involved is usually the exact opposite of that manifest in the reactive trait. Similarly, emotions that have been sublimated by changes in objects or direction may be misinterpreted unless the history of that trait is understood.

The purpose of this paper is to trace the evolution of the various character traits, as expounded by the researchers in psychoanalytic characterology, and to indicate their frequency and significance in the migraine cases of this study. It is emphasized that it is the pattern of numerous character traits pointing to the same mechanisms that signifies the probable conflicts, frustrations, or gratifications the patient is dealing with. The method of character interpretation described here is not as specific as psychoanalysis, but can perform as a "qualitative" study sufficient for most cases of migraine. In refractory cases the "quantitative" study of psychoanalysis is recommended.

The subjects of this study consisted of 100 adults, 65 women and 35 men. The durations of migraine were as follows: less than 1 year, 11 patients; less than 5 years, 36 patients; over 10 years, 53 patients, and over 30 years, 14 patients. The migraine appeared in 7 patients before puberty, in 35 patients during puberty, in 48 patients during young adulthood, and in 10 patients after the age of 40. The criteria for diagnosis were those which Wolff has formulated in his monograph [6] and with which other investigators concurred.[12] It is recognized that clinical diagnoses have a few unavoidable errors, but a large series of patients reduces the importance of such rare conditions as may mimic migraine.

The chief task of the ego in the oral period of life is to procure gratification of narcissistic needs. The narcissistic needs at this stage are manifested as a need for love and approval from external sources, mainly the parents. Abraham [9] observed that an undue frustration of these needs or an unusual gratification of them resulted in an exaggerated yearning for love and approval in later life. This unusual sensitiveness to love and approval was found in all the patients of this study. Practically every patient was consciously aware of this need. The rare patient who denied the need indicated by his activities that the denial was a reactive trait.

To secure these very much needed narcissistic supplies, the orally fixated person develops character traits to insure the gaining of these supplies and the avoidance of their loss. Gaining love is done initially by compliance with the demands of the parents and later with those of society and the superego. The following oral traits [9] were found to a degree in all patients of the migraine group studied.

Traits evolved primarily about the gaining of narcissistic gratification:

1. Starting tasks right away
2. Doing tasks quickly
3. Doing tasks in the best way possible
4. Being busy all the time
5. Restlessness
6. Energetic conduct of activities

Traits evolved about the avoidance of loss of narcissistic gratification:

1. Persistent wariness and alertness
2. Consideration of all the possibilities of success
3. Apprehensiveness of possible failure and criticism
4. Anxiety during impending failure and criticism

Traits evolved about the loss of narcissistic gratification:

1. Disappointment from slightest loss of self-esteem
2. Depression after failure or criticism
3. Marked need for love and approval

The need to possess love and approval can be displaced by the process of sublimation to an inordinate desire to possess objects, knowledge, power, and prestige.[9] Fulfilling these ambitions was one of the main sources of gratification of the narcissistic needs in the migraine group studied. Because the gratifications so produced allayed feelings of disappointment and resentment, during periods of such distress, the patients often buried themselves in their work and worked their troubles off. Disturbances in their ability to acquire the equivalents of love and approval often permitted latent hostility to appear near the surface, and anxiety or the attack of migraine commonly resulted.

Another sublimation of oral erotism is the reversing of the flow of objects and love from receiving to giving, namely, an intense desire to give objects, knowledge, advice, and service.[9] These traits Abraham considered an identification with the bountiful mother, but it has other determinants in guilt-alleviating mechanisms in the later ambivalent stages.[11] The choice of vocation and avocation was strongly influenced by these oral needs to give and serve, in the fields of teaching, social work, nursing, and the like. A fondness for giving gifts to loved persons was present in almost all the cases. This trait is derived also from sublimations of anal erotism, to be mentioned subsequently.

In the development of the child, his program of narcissistic gratifications becomes complicated by the needs to express his aggressive or self-assertive instinct. This problem becomes manifest in our society toward the end of the oral period, when weaning and training of the child produce feelings of hostility toward those who frustrate its narcissistic desires and who thwart its budding self-assertiveness. This stage is referred to as the oral sadistic period and begins the state of ambivalence, which persists until final genital maturity occurs.[9]

Abraham[9] considered the character traits evolving in the oral sadistic period to be envy, jealousy, covetousness, hostility, friendlessness, sarcasm, and ambivalence. Very few of the patients of this study showed the first five of these traits, rather the exact opposites. A superficial accommodating and tolerating attitude, amiability, politeness, unselfishness, gentleness, and inhibition of aggressiveness were usually present. The last trait, the inability to show hostility openly, was present in 93% of the patients. But the reactive nature of these traits was readily apparent in the tension associated in maintaining these traits under stress and the periodic breakthrough of the underlying oral sadistic emotions in actions and dreams. In almost all cases ambivalence toward parents or family was elicited, although this was usually initially voiced with hesitancy. Once the inertia was overcome, however, the resentments were voiced in profusion. In a few the ambivalences were unconscious but were evident in dreams. A common escape of the suppressed hostility was in sarcasm, which some had developed as the chief medium of expressing aggressiveness. On the whole, the oral aggressiveness was not only suppressed, but doubly suppressed by reaction formations.

It is sometimes difficult to evaluate whether the aggressiveness manifested is primarily oral, anal, or genital in origin. Abraham[9] considered that anxiety indicated inhibited oral aggressiveness, guilt-inhibited anal sadism, and shame-inhibited genital

hostility. The people with migraine in the group, as they accumulated resentments, reacted chiefly with anxiety when these resentments were on the verge of breaking through. Anxiety reactions were the commonest of the neuroses in the group, being manifest in 35%.

The chief method of alleviating anxiety at this period is to gain love and approval from its objects.[13] The "good and loving" parent refutes the threats of the "bad and punishing" parent. The more the ambivalence, the more the anxiety, and the more stress is placed upon gaining love and approval from objects in the world. Securing relief from such anxiety contributes much to the development of the intense need for love and approval which is the outstanding trait of the migraine patients in this study.

A predisposition to depressions is considered to indicate fixation at the oral sadistic stage.[9] The hostility which is experienced by the orally fixated person is not only inhibited but turned on the ego in a disguised attack on the love object. Much of the depressed moods of the migraine person is probably due to this mechanism. Frank depressive reactions were present in 22% of the group, occurring at the involutional period in 10%.

Following closely the oral sadistic period is the anal stage. At this time the ego's problem is to secure pleasures centered about the product and the act of defecation and to develop and control its self-assertive instinct despite the many viscissitudes it is subject to in training for obedience and sphincter control. Jones[10] developed an extensive classification of anal character traits, which Abraham[9] confirmed in his studies. The formulations of Jones are followed below.

The largest group of anal characters are considered to have evolved in response to the self-assertiveness of the individual in attempting to maintain control of the act in opposition to parental aims. Of this group, the following eight traits were observed consistently in each patient of the group:

1. Resentment of being under pressure
2. Insistence of one's rights and dignity
3. Resentment of any form of injustice
4. Intolerance of being cheated of money
5. Insistence on punctuality
6. Resentment of being forced to wait
7. Aversion to owing anyone an obligation
8. Insistence on planning one's own activities

The second group of anal characters is a mixture of narcissistic and assertive elements, the desire to maintain control of the act in order to get as much pleasure out of it as possible. All six traits were present in every patient.

1. Sensitiveness to interference
2. Persistence in an undertaking
3. Thoroughness
4. Superiority feelings
5. Perfectionism
6. Self-willedness

13. Klein, M.: The Psycho-Analysis of Children, London, Hogarth Press, Ltd., 1933, Chap. 10.

The third group of anal traits is interpreted as sublimations or reactions to the pleasure derived in the two phases of anal erotism—that of giving up and of retaining the product. Each patient of the study had the majority of the sublimations and all of the reactions listed.

Sublimations

1. Economy
2. Desire to collect coproic symbols, such as money, coins, stamps, books, jewelry, and art
3. Great affection for children
4. Domination of loved or possessed objects
5. Interest in painting, printing, photography, cooking, engraving, or sculpturing
6. Predominance of giving love, gifts, and good deeds

Reactive traits

1. Cleanliness
2. Orderliness
3. Reliability

The amount of anal fixation has a decided effect on the personality structure. The influence of oral narcissism is diminished, and character disturbances due to strong oral fixation, such as schizophrenia or drug addiction, were not present in any of the patients.

As mentioned above, feelings of guilt are considered to inhibit anal aggressiveness, and persons with as much fixation in the anal period as had the migraine patients of this study might be expected to have a predisposition to guilt feelings or to manifest reactive traits to guilt. This was found to be true in the majority of cases. Feelings of hostility when experienced or expressed commonly resulted in guilt. This was usually carried to an extreme in regard to the family. Mechanisms to relieve guilt are many, but two were found very commonly in this study—a compulsion to give and serve others and a compulsion to produce work. Interference with these mechanisms of restitution would result in latent guilt becoming manifest in such cases. Withdrawal from an occupation, as during week ends, vacations, or intercurrent illness, often intensified conflicts.

A closely related guilt-relieving mechanism is considered to be the syndrome of colitis. The bowel movements are evaluated as unconscious giving of restitution for hostile feeling.[14] Colitis was found in 18% of the patients in the group.

One of the important effects of ambivalence, at its peak during the anal period, is that on superego formation. The actual standards of the parents destined to form the nucleus of the superego are modified by the child's own attitudes. Hostile feelings of the child are projected on to the parents. Even a lenient parent may be considered severe by an ambivalent child. It is these distorted impressions of the parents that the child incorporates into the superego.[15] This process makes the superego of an ambivalent person a forbidding, exacting, ultramoral force, which has a powerful control of the ego's self-esteem.

The marked dependence of an orally fixated character on its superego puts the person with such a severe superego in a particularly unfavorable situation. Such a

14. Alexander, F.: The Influence of Psychologic Factors upon Gastro-Intestinal Disturbances, Psychoanalyt. Quart. **3**:501 (Oct.) 1934.

15. Freud, S.: Civilization and Its Discontents, New York, Robert O. Ballou, Publisher, 1930, p. 115.

taskmaster is never satisfied, contributing greatly to the state of tension and apprehensiveness common to the group. This situation also accounts for much of the feelings of inferiority and inadequacy that are often present, the patients' actual accomplishments to the contrary. Even when society approves of them, they could be disappointed and consider themselves to have failed because of the distorted standards of the superego.

In an attempt to escape the internal tensions, the individual reprojects the rigid demands of the superego on to society,[13] resulting in a feeling of being under inordinate pressures by people who demand the absolute best at all times and who never seem to be pleased, situations which he objectively incorrectly evaluates. This situation interferes with the program of narcissistic gratification and results in the development of a large amount of social anxiety, which further handicaps the ego.

The tasks of the ego in the genital stage of development are to overcome the narcissism, the ambivalence, and the hostility of the oral and anal periods, to resolve the fears and ambivalences produced by the Oedipal situation, and to evolve in their place a mature object love. Such unambivalent object love leads to full sexual potency and gratification, to a fondness and devotion to the parents, and eventually to a friendly and well-wishing attitude to the people about and to the whole environment. Failure in these tasks is evident in frigidity and impotency, neurasthenic reactions, anxiety and conversion hysterias, many sexual aberrations, and disturbed social relationships.[11]

Despite the oral and anal fixations, the majority of the migraine persons in the study were able to reach a mature sexual adjustment, 74% of the women and a similar rate for the men. The development of a mature social feeling, however, was rarely noted, primarily because of the ambivalences present. Neurasthenic reactions were present in 18% of the patients, and the hysterias, in 5%. No cases of sexual perversions were disclosed.

COMMENT

From the foregoing data, it is evident that both the love instinct and the aggressive instinct are well developed in persons with migraine. Yet the basic incompatibility of these instincts requires that they be alternately expressed or that one become dominant and the other inhibited. In migraine persons of this study, the love instinct was dominant in 93%, and hostility was inhibited habitually in various degrees, 49% showing it to no one and the remainder to a selected few. As long as this compromise could be maintained, little conflict resulted. However, when the narcissistic or genital needs were frustrated too much or the aggressiveness was stimulated, the equilibrium was disrupted by the increase in hostility. Since the superego prohibits the conscious expression of most hostility to loved objects, the hostility remained largely conscious, but suppressed. A more prohibitive superego relegates the hostility to the unconscious. The seven patients who ordinarily expressed angers freely also expressed other emotions freely as well. They began to have migraine when restrictions were placed on their usual channels of expression.

An emotion, even though it is inhibited, consciously or unconsciously, produces somatic changes. A typical example is the vasomotor phenomena of the anxiety attack in response to unconscious fear. There are a variety of vasoconstrictor and vasodilator responses in the body to anger. One could explain the migraine attack as the physiologic autonomic manifestations accompanying inhibited hostility. Alex-

ander [16] classified such phenomena as a vegetative neurosis. He emphasized that such phenomena do not diminish the underlying conflict, that the mechanisms of conversion are necessary to mitigate the conflict and thus be of utility to the individual. The formulation of Fromm-Reichmann that migraine is an unconscious attack on the incorporated love object, which is consciously loved and protected from attack by the superego, interprets migraine as a conversion neurosis. So interpreted, the migraine attack expresses partially a prohibited instinctual desire, anger, but at the same time satisfies the superego by punishing the ego with pain, thus accomplishing the dualistic purpose of the neurotic compromise. My impression is that migraine has elements of both a vegetative and a conversion neurosis. Further psychoanalytic research, particularly into the question of whether the attack of migraine produces some relief of hostility, is needed before further conclusions can be made.

The dynamic concepts of migraine should account for some of the characteristic timing of migraine. The frequent onset in puberty of migraine (35% in this series) coincides with the marked increase in self-assertion of adolescence, which would intensify the individual's ambivalence. The onset in earlier or later periods in each case could be traced to intense frustrations in family, marriage, and occupation, which would intensify the aggressiveness of the individual. The precipitation of migraine at the involutional period (9% in this series) also coincides with the definite increase in aggressiveness characteristic of this period.

The interesting phenomena of migraine disappearing at the involutional period in several of the cases was associated with an increase of aggressiveness of such degree that the whole formula of love-inhibiting aggression was reversed.

The occurrence of migraine during sleep (10% in the series) and immediately on awakening (19% in the series) fits in well with the concept that unconscious hostility, less controlled during the dream life, can be mobilized and the migraine attack result. This type of periodicity was usually associated with deep-seated unconscious ambivalence toward the family.

The technique of psychotherapy using the foregoing data and mechanisms will be discussed in a subsequent paper. It is similar to the techniques described by Slight [6] and Wolff.[6] In general, the initial goals are to build up the ego by reducing situational frustrations and increasing the gratifications. By reviewing pertinent incidents of the patient's life, an opportunity is given to develop a more mature perspective of these incidents to replace the defensive attitudes formed in childhood which have continued in a stereotyped manner into adulthood. A compromise is sought between the ego and the superego, to agree upon common standards and to set up an ego ideal that takes into account the demands of the adult reality. This will permit the transformation of disturbing reactive traits into genuine ones of the sublimation type, which is required for full emotional maturity.

After therapy, patients who had successfully modified their conflicts showed changes in their character patterns, their neurotic manifestations disappeared, and their migraine remitted. These cases served to illustrate that character is a changeable thing, that it mirrors the conflicts, frustrations, and gratifications of the individual, and that changes in these underlying forces are reflected in changes of character. Abraham [9] emphasized this throughout his classic articles on character.

16. Alexander, F.: Fundamental Concepts of Psychosomatic Research, Psychosom. Med. **5**:205 (July) 1943.

The prevention of migraine is a challenge, for it is estimated that 1 out of 12 persons suffer with it.[17] I believe it is the modification of parental attitudes, particularly with sensitive, strong-willed children, that will reduce the frequency. A parent who is undemonstrative of affection, who demands an inhibition of aggressiveness in the family, or who is rigid and strict in discipline and training is the potential nemesis of a child with an innately strong need for love and self-assertiveness. Such combinations result in fixations in the oral and anal periods that produce the persistent ambivalence, of which migraine is but one of the by-products. In the group studied, 80% of the patients considered one or both parents undemonstrative of affection, and 89% considered one or both parents strict in training and discipline. One or the other of these two parental attitudes was present in all but one case. The adjusting of parental attitudes to the individual child's needs will be attacking migraine at its source.

SUMMARY

The character patterns of 65 women and 35 men with migraine were studied according to the principles of the psychoanalytic concepts of character formation. The persons of the group consistently possessed traits that indicated a marked narcissism, as well as a strongly developed aggressive instinct. Lack of demonstration of affection or strictness of training by the parents frustrated these needs, resulting in ambivalences and the development of an ultramoral and rigid superego. In all the patients the migraine attack began when hostilities accumulated beyond the individual's capacity for tolerance of frustration. Migraine is considered a vegetative neurosis, the physiologic vasomotor manifestation of suppressed or repressed hostility, initially directed specifically toward the family and later to frustrations in general.

6249 Langdon Ave.

17. Wolff,[6] p. 255.

FATALITIES IN INSULIN THERAPY OF THE PSYCHOSES

Analysis of Eight Cases

A. E. SCHEFLEN, M.D.
E. R. REINER, M.D.
AND
W. W. JETTER, M.D.
BOSTON

ASSOCIATED with the Massachusetts Department of Mental Health is an agency designated to investigate certain deaths occurring in psychiatric hospitals. In the last 11 years eight deaths incident to insulin coma or subcoma therapy have been reviewed: four in state hospitals, two in private institutions, one in a veterans hospital, and one following treatment in a patient's home.

Numerous fatal insulin reactions have been reported.[1] Most of the clinical papers have been concerned with the events of the final coma. Little attention has been paid to factors, other than overt organic diseases, which give warning of an untoward reaction. Certain clinical features and aberrant physiological responses occurring prior to the fatal reaction, and of possible value in prognosticating it, are presented in this report.

CASE 1.—*A white man aged 47, with a diagnosis of schizophrenia, paranoid type, was treated with insulin coma. On the 63d treatment, 28th coma, he had an apparently normal coma, with a dose of 360 units of insulin. Five minutes before termination was scheduled, he suddenly became pulseless and apneic and died immediately.*

The patient had had influenza in 1918 and otitis media in 1944, with permanent bilateral hearing loss. The psychiatric history revealed neurotic and schizoid traits from early childhood.

The psychosis developed insidiously in 1947. In January, 1948, he was admitted to a psychiatric hospital, where a diagnosis of schizophrenia, paranoid type, was made. The patient was well nourished and presented no abnormalities on physical examination. A cardiologist reported no heart disease, and the blood pressure, pulse, and electrocardiogram were recorded as normal.

Shortly after his admission, electroshock therapy was instituted, and tubocurarine was used. During the fifth shock, with 3.5 cc. of tubocurarine chloride, he had dyspnea, cyanosis, and then respiratory arrest. When artificial respiration and oxygen were administered, respiration and color improved. For the next hour he showed generalized tremor, signs of atelectasis at the base of the right lung, and a shaking chill. An hour later he had apparently recovered. Electroshock therapy was continued without curare for a total of 22 treatments. No other unfavorable reactions occurred.

Senior Physician, Research Service, Worcester State Hospital (Drs. Scheflen and Reiner); Professor of Legal Medicine, Boston University School of Medicine, and Director of the Division of Legal Medicine, Massachusetts Department of Mental Health (Dr. Jetter).

1. Lester, D.: A Study of Prolonged Coma Following Insulin Shock, Am. J. Psychiat. **95**:1083, 1939. Horwitz, W. A.; Blalock, J. R., and Harris, M. M.: Protracted Comas Occurring During Insulin Hypoglycemic Therapy, Psychiatric Quart. **12**:466, 1938. Binzley, R. F., and Anderson, J. L.: Prolonged Coma in the Insulin Treatment of Dementia Praecox, ibid. **12**:477, 1938.

He continued to be hallucinated, deluded, seclusive, and paranoid. Twenty-two months after electroshock treatment was completed a course of insulin coma therapy was started. After 11 weeks of therapy a laceration of the hand, sustained in reacting to a hallucination, necessitated interruption of the treatment. Sixteen days later it was resumed. The 63d treatment and 28th coma, given three weeks later, was fatal.

He had received amobarbital sodium (amytal®) (0.18 to 0.3 gm.) just before the onset of each coma. No other noteworthy events occurred, and none of the comas prior to the fatal one was unusual.

On the fatal day he received 360 units of insulin, to produce his 28th coma. There were no signs indicating a coma of unusual depth. After 50 minutes of coma, his pulse was noted to be 60 per minute, regular, and of good quality. At this time his color was nomal, but five minutes later he had become cyanotic and no pulse was obtainable. Artificial respiration was begun and continued for 55 minutes, without effect. He remained pulseless, cyanotic, and apneic. Without effect were four intravenous injections of glucose solution, totaling 75 gm.; administration of ascorbic acid, 1.0 gm.; intravenous injections of epinephrine hydrochloride (1:1,000), 1 cc., and caffeine and sodium benzoate U. S. P. (1 gm.), and intracardiac administration of epinephrine hydrochloride, 2 cc. of 1:1,000 solution.

Comment.—1. The patient reacted atypically to both curare and insulin.

2. The course of therapy was interrupted.

CASE 2.—*A white man aged 26, with a diagnosis of schizophrenia, paranoid type, was treated with insulin coma. The fatality occurred during the 12th treatment and third coma. Ten minutes after the onset of coma, the pulse and respiratory rates increased markedly. Apnea and sudden death followed.*

This patient had had enuresis and frequency of urination since childhood. Repeated examinations had shown occasional albuminuria, but no other evidence of urological disease had been demonstrated. The presence of other medical disease or psychiatric symptoms was denied. The family history was not significant.

When he was 21, acne developed. Shortly thereafter there was sudden onset of a psychosis, with delusions and exhibitionism. Physical examination on his admission showed seborrheic dermatitis of the face, clammy extremities with excessive perspiration, a pulse of 100 beats per minute, and a blood pressure of 138/70 mm. Hg. After seven electroshock treatments the patient's condition improved, and he was released two months after admission.

He made an adequate adjustment for two years but then became increasingly withdrawn, deluded, confused, and paranoid. On readmission, at the age of 26, he was relatively well nourished. At that time there was a "very slight systolic murmur at the base," probably functional.

Physical, neurological, and laboratory studies otherwise revealed nothing abnormal. An electrocardiogram and a roentgenogram of the heart and lungs were normal.

A few days after admission he received a test dose of 25 mg. of corticotropin (ACTH). Three minutes later he fell to the floor, dazed but not unconscious. He recovered promptly.

Three weeks after admission he began a course of intravenous injections of ether (2.5%). He received a total of 19 treatments, completing the course on Aug. 1.

On Aug. 15 insulin therapy was begun. Six treatments were given, with the following doses: 20, 80, 160, 250, 300, and 450 units. No coma or untoward reaction resulted. The patient was so uncooperative and resistive that therapy was discontinued on Aug. 22. Subsequently, he received a course of five electroshock treatments. Between Aug. 29 and Sept. 12, after an interval of 20 days, insulin coma therapy was resumed, with a 600-unit dose. He remained unusually resistive to the treatment, regularly refusing to go to the insulin uni.. He continued to express depressive, nihilistic ideas and to show suicidal intent. He complained that he was being tortured by the therapy and showed extreme fear. On Sept. 14 and 15 he received daily doses of 800 units. On Sept. 18 he had his first coma, after 900 units. The following day his second coma occurred, with the same dose. On Sept. 20, after 700 units, the third, and fatal, coma occurred.

It was further observed that the patient's morning rectal temperature prior to the beginning of his daily therapy was often as low as 97.0 to 97.4 F.

Several minutes before the fatal coma began (2½ hours after the intramuscular injection of insulin) the vital signs were normal. Ten minutes after the onset of coma the pulse reached 148 per minute. The respirations were labored, at a rate of 40 per minute. Aspiration yielded little mucus. Five minutes later apnea occurred. Oxygen and artificial respiration were administered for 25 minutes. At that time there were no cardiac sounds. Epinephrine hydrochloride, 2 cc. (1:1,000), was injected into the heart, without benefit.

Comment.—1. The patient showed pronounced fear and violent resistiveness.

2. There were signs of overactivity of the sympathetic nervous system.

3. Insulin therapy was begun two weeks after a course of intravenous injections of ether.

4. The patient had had a syncopal reaction to a test dose of corticotropin.

5. Insulin therapy was interrupted. After an interval of 20 days, he received high doses, 600 to 900 units, of insulin.

6. The morning rectal temperatures were often as low as 97.0 to 97.4 F.

CASE 3.—*A white man aged 25, with a schizophrenia, paranoid type, was treated with insulin coma. He failed to respond at termination of the eighth treatment and third coma. He continued in prolonged coma with torsion spasms, tachycardia, stertorous breathing, periods of apnea, and elevation of temperature to 104 F. After 42 hours, death occurred in peripheral circulatory collapse, with apnea preceding cardiac failure.*

He was said to have had diphtheria three times during childhood. Five years prior to admission he had sustained a head injury, requiring about four months' hospitalization. Further details about this hospitalization were not available, but subsequent neurological examinations did not reveal clinical residua. The medical and family histories were otherwise noncontributory.

Immediately prior to the Normandy landings of 1944 the patient suddenly manifested psychotic symptoms. He was evacuated to the United States and was consequently discharged from the Army. He apparently recovered, but a year prior to his admission he again became confused. In the month preceding admission he lost 30 lb. (13.6 kg.) in weight. For this reason he was admitted to a diagnostic hospital, where the medical, neurological, and laboratory findings were without significance.

On admission to a private sanatorium, he was confused, withdrawn, and deluded. Physical examination revealed no abnormalities except for evidence of recent loss of weight. During the first month of hospitalization he failed to improve or to gain weight and was then placed on insulin coma therapy.

He received intramuscular injections of insulin daily in the following dosage: 20, 40, 60, 80, 100, 120, 130, and 140 units. On the fourth day of treatment all pulse rate determinations were between 54 and 60 per minute, but no other untoward signs were observed. These pulse rates were significantly lower than those found during any of his other seven treatments. On the eighth treatment the patient had his third successive coma. There were no abnormalities until routine termination, after 70 minutes of coma, was attempted. He failed to respond to administration of 95 gm. of glucose by gavage, and within the following 20 minutes 30 gm. more glucose was administered intravenously. Caffeine, epinephrine, and nicotinamide were of no avail. At this time the blood sugar was 195 mg. per 100 cc. During the rest of this day he continued in prolonged coma, with convulsive jerking, stertorous breathing with periods of apnea, a pulse rate of 120 per minute, and a rise of temperature to 104 F. No evident benefit was produced by transfusions of 500 cc. of whole blood and 500 cc. of plasma, intravenous administration of saline and dextrose solutions, and intravenous injection of 20 cc. of cytochrome C. The blood sugar level in the late afternoon was 580 mg. per 100 cc. The blood potassium was 5.2 mg. per 100 cc.; the blood chlorides, 119 mg. per 100 cc., and the blood sodium, 158 mEq.

The following day, sensitivity to pain increased, and the pupils reacted slightly. There were occasional tonic attacks of rigidity of the trunk and extremities, alternating with athetoid movements. Moderate pitting edema of the face, sacrum, and thoracic wall developed. Injection

of cytochrome C was twice repeated, and intravenous use of saline solution and administration of glucose by gastric tube were continued.

About 40 hours after the onset of coma there was abrupt development of cyanosis and circulatory collapse. Breath sounds were absent over the bases of both lungs, and no rales were heard. The apical cardiac beat was audible for several minutes after respiratory arrest.

Comment.—1. In the month before admission the patient lost 30 lb. (13.6 kg.) of weight, and he was severely emaciated on beginning treatment.

2. During the fourth treatment all pulse rate determinations were between 54 and 60 per minute. During other treatments he had no bradycardia.

3. The significance of the history of diphtheria and head injury could not be assessed.

CASE 4.—*A white man aged 27, with a diagnosis of schizophrenia, hebephrenic type, was treated with insulin coma. After the 12th treatment, third coma, he failed to respond to termination with administration of glucose. Ten minutes later, during the insertion of a Levin tube, he suddenly became cyanotic and pulseless.*

There was no known history of significant psychiatric or physical illness in childhood or adolescence. While in the armed services, he married but made a poor adjustment, characterized by suspiciousness and abusiveness. After the birth of the first child his symptoms progressed, requiring his admission to a veterans hospital for mental disease. There he received electroshock therapy and was discharged as improved about three months later. Three and a half years later he was admitted to a private psychiatric hospital because of delusions and hallucinations. On his admission, the physical examination, laboratory tests, and x-ray studies of the chest and spine were noncontributory.

Three days after his admission a course of insulin coma therapy was started. He received 12 treatments without interruption. Electroshock therapy was given with the 2d, 6th, 8th, and 11th insulin treatments. Coma resulted from the 7th, 11th, and 12th treatments, with 500, 450, and 450 units of insulin respectively. The last treatment was fatal.

The ninth treatment produced a grand mal seizure, and one hour after termination further glucose was needed for relief of "after-shock." During the second coma the pulse rate was 64 per minute, considerably lower than any other pulse count recorded for this patient.

During the entire course of therapy, all rectal temperatures taken prior to the injection of insulin were low, ranging from 97.0 to 96.4 F. Blood pressures ranged from 100/70 to 80/50, with an average of 84/56 for the treatment period.

Thirty minutes after termination of the second coma, the patient relapsed into a deep coma, which was successfully terminated by 100 gm. of glucose. On the last two treatment days, when the termination was difficult, the patient had received amobarbital sodium, 0.25 gm.

On the 12th treatment day the patient had a coma after receiving 450 units of insulin. The coma was uneventful and was described as "medium" in depth. It was allowed to continue for one hour. Termination was attempted with intravenous administration of 37 gm. of glucose. Ten minutes later 13 gm. more was given. At this time, during the insertion of a Levin tube, the patient suddenly became cyanotic and pulseless. Resuscitation measures were of no avail.

Comment.—1. Throughout all treatments the pulse rate always exceeded 80 per minute, but during the treatment on the day prior to the fatal coma the pulse rate was 64 per minute.

2. The morning temperatures and blood pressure readings were low (96.4 and 80/50) throughout treatment.

3. In all three comas the patient relapsed again into coma after termination.

4. The day before the fatal coma, termination was difficult after 450 units of insulin. The same dose was administered on the fatal day.

5. Death occurred suddenly while a Levin tube was being inserted.

CASE 5.—*A white woman aged 21, with a diagnosis of schizophrenia, hebephrenic type, was treated with insulin coma. On the fifth treatment, third coma, the attempt at termination was unsuccessful. During the next hour dyspnea, rapid, thready pulse, dilated pupils, and torsion spasms developed. During the second hour of protracted coma, pulmonary edema developed, and the patient died suddenly, with cardiac arrest, during an attempt at laryngoscopic aspiration.*

The patient had been raised in a strictly religious home, by a rigid mother and a tyrannical father. Hospitalization resulted from sudden onset of confusion, sexual delusions, and hallucinations.

On her first admission she was apprehensive, pale, and undernourished. There were no other significant findings. She was treated with insulin coma, without untoward reactions. After the 18th coma, on the insistence of relatives, therapy was discontinued, and she was removed from the hospital, against advice.

During the next 18 months she remained psychotic but was kept at home by the family. For five months before readmission she ate inadequately, although she was overactive and often sleepless.

On readmission she was severely emaciated, weighing 86 lb. (39 kg.), and so weak that sitting up was difficult. Physical examination showed "warty" lesions at the angles of the mouth and numerous ecchymoses of the body. There were a "soft apical systolic murmur" and "an arrhythmia." The pulse rate was 60 per minute. An electrocardiogram three days later showed only sinus arrhythmia with a normal P-R interval. It was decided that the patient did not have heart disease. The blood sugar levels in an insulin tolerance test were reported as follows: fasting specimen, 45 mg. per 100 cc.; 15-minute specimen, 39 mg.; 30-minute specimen, 52 mg., and 1-hour specimen, 43 mg.

The hemoglobin measured 10 gm. per 100 cc. An electroencephalogram showed a mild, but definite, arrhythmia with asymmetry of the right cerebral hemisphere. Roentgenograms of the skull were considered normal.

Two days after admission she was placed on a regimen of 10 units of insulin before meals. This was discontinued after two weeks. Five days later insulin coma therapy was begun. On five successive days she received 20, 40, 80, 70, and 70 units of insulin, respectively. The last three doses produced coma. In each of these comas the pupils were constricted, despite previous atropinization (0.86 mg.). Phenobarbital (luminal®), 0.1 gm., had also been given before each coma. The first coma was difficult to terminate by gavage but was ended satisfactorily by intravenous administration of glucose. The preinjection rectal temperature before the last two comas was 97.0 F.

The third coma was fatal. At 9 a.m. the pupils were reported to be constricted, despite atropinization. An hour later an attempt to terminate coma by gavage was unsuccessful. Twenty-five minutes later intravenous use of glucose was begun and continued at short intervals over the next 15 minutes until 125 gm. had been given. At 10:30 a.m. she had dyspnea and a thready pulse of 120 to 140 per minute. The pupils became dilated, and torsion spasms began. Within the next 15 minutes, the pupils showed alternate dilatation and constriction, and there were alternate flaccidity and rigidity of the extremities. Morphine, aminophylline, and application of tourniquets to the extremities were not effective. At 11:30 a.m. the pulse rate varied from 140 to 160 per minute, and the signs of pulmonary edema developed.

Fifteen minutes later, during an attempted laryngoscopic aspiration, acute cardiac failure occurred. Intracardiac injection of epinephrine and artificial respiration had no effect.

Comment.—1. The patient was severely undernourished, with weakness and anemia. The "warty" lesions at the corners of the mouth and the ecchymoses suggested avitaminosis.

2. There were encephalographic abnormalities of unknown significance.

3. A year and a half previously the patient had had 18 insulin coma treatments.

4. The preinjection rectal temperature was 97.0 F. on the last two coma days. On admission the pulse rate was 60 per minute.

5. The pupillary constriction which was present during all three comas, despite atropinization, was construed as a sign of unusually deep coma. The first coma was difficult to terminate.

6. Death occurred suddenly after laryngoscopic aspiration, suggesting the possibility of a vagovagal reaction.

CASE 6.—*A white man aged 27, with a diagnosis of schizophrenia, paranoid type, was treated with insulin coma. On the 54th treatment, 18th coma, administration of 340 units of insulin produced only a subcoma. At the time of termination the pulse rate and temperature were increased, and after termination the patient remained confused. Two hours later pulmonary edema developed, and he returned to coma, dying four hours after termination of coma.*

The patient had been shy, moody, seclusive, stubborn, and sensitive since childhood. The past medical history was reported as normal except for a tonsillectomy and rhinoplasty at the age of 25. He gradually acquired the delusion that an odor from his body influenced other people.

On admission he was preoccupied, deluded, inappropriate in affect, and withdrawn. Physical examination showed good nutrition and a normal condition except for chronic rhinitis and cardiac murmurs. The latter were described as "a medium loud apical systolic and a slight basal systolic murmur." There was "a rather marked sinus arrhythmia." No cardiac enlargement or other abnormality was noted on clinical and roentgenologic examinations. Nasal obstruction and rhinorrhea, attributed to recurrent infections of the upper respiratory tract, were present almost continuously throughout hospitalization.

Six weeks after admission, insulin coma therapy was begun. The patient received 54 treatments without interruption. On the 10th treatment the first coma occurred, with a dose of 220 units. During the next 14 treatments coma occurred daily. Afer this the patient became refractory to insulin. In the next 22 treatments he had only three comas, and during the last 18 treatments, only one coma. Throughout the therapy period, of 54 treatments, he responded only 18 times with a therapeutic coma. Morning pulse rates were frequently between 60 and 64 per minute.

There was, however, a definite tendency for insulin reactions to occur after termination of the treatments. During the course of insulin therapy he had eight "after-shocks," occurring after both coma and subcoma reactions. Each of the last three treatments was followed by "after-shock," the last proving fatal.

On the morning of the fatal day the rectal temperature was 98.6 F. He received 340 units of insulin but did not have a coma. During the last hour before termination the respiration rate was 26 per minute, although he was quiet. Treatment was otherwise not remarkable until termination, at 11:15 a.m., at which time his rectal temperature was 103.6 F. He received 75 gm. of glucose intravenously, but remained mildly confused. His color and pulse were good, but at 1:15 p.m. there developed "drooling from the mouth" of blood-tinged fluid, labored breathing, and generalized rales. At that time the blood sugar was reported to be 14 mg. per 100 cc. At 1:30 p.m. he was in coma, and he did not respond to 125 gm. of glucose given intravenously. Postural drainage, oxygen administration, aspiration, and artificial respiration failed. Intracardiac administration of epinephrine, nikethamide, and atropine was also without benefit.

Comment.—1. The patient was rather refractory to insulin, having only 18 comas in 54 treatments.

2. There was a tendency for insulin reactions ("after-shock") to occur, and the last was fatal.

3. Preinjection pulse rates were unusually low.

CASE 7.—*A white youth aged 16, with a diagnosis of schizophrenia, paranoid type, was treated with insulin coma. He had his first coma with the ninth treatment, after 2,000 units of insulin. The following day the dose was reduced to 500 units, but after 30 minutes of coma an attempt at routine termination was unsuccessful. He remained in protracted coma for eight hours, then died suddenly in respiratory arrest.*

The patient had attended special classes for retarded children, beginning with the third grade. The parents were described as quarrelsome, unaffectionate, and abusive. The past medical history

was noncontributory. The first admitted abnormal behavior occurred a week before his admission, when he complained to the police that he would be killed by his parents. He was admitted to a psychiatric hospital, requesting that he be punished for his sins.

On admission he showed affective flattening, persecutory delusions, and grandiosity. On physical examination the abnormal findings were evidence of childhood rickets, a "split mitral first sound," and tracheobronchitis. He was asthenic but not undernourished. A roentgenogram showed a widened, prominent aortic arch. The electroencephalogram was abnormal, with slow activity indicating previous brain damage.

After admission he received 20 electroshock treatments, without improvement. He participated in ward activities but remained paranoid and preoccupied. For a period of 10 days he received about 50 units of insulin daily and then was placed on insulin coma therapy. Insulin was administered intramuscularly on successive days, in the following doses: 50, 100, 200, 400, 800, 1,600, 1,600, 1,600, 2,000, and 500 units. The second 1,600-unit dose produced a subcoma reaction. The 2,000-unit dose produced a third-stage coma, after which the patient was "sluggish." During the last few days of treatment he had appeared lethargic and inactive after treatment. During the night preceding the fatal treatment the patient was confused, requiring bed sides, but he appeared alert on the morning of the final treatment. No other evidence of "after-shock" or difficulty in termination had been observed. He received phenobarbital (60 mg.) twice daily throughout treatment. Daily vital-sign determinations were not regularly recorded. The patient was fearful of insulin treatment and preoccupied with the idea that he would be killed.

On the fatal day the patient went into coma three hours after the injection of 500 units of insulin. Pulse and respiration rates were normal, and untoward signs were not observed. Thirty minutes later termination was attempted according to schedule. Return to consciousness was not effected by administration of 250 gm. of glucose by gavage and 50 gm. by intravenous injection.

During the next six hours 2,500 cc. of 10% glucose solution was administered by clysis. By lavage, the stomach contents were repeatedly removed and replaced with eggnog solution. The blood pressure gradually rose to a high point of 170/104 mm. Hg, and the pulse rate gradually fell to a low of 72 per minute. The patient remained unconscious. About seven hours after the unsuccessful attempt at termination, an increasing amount of "mucus" began to obstruct the respiratory passages, requiring repeated aspiration. An hour later, during aspiration, apnea occurred. The heart beat was audible several minutes later. Intracardiac administration of epinephrine, nikethamide, and caffeine and artificial respiration were of no avail.

Comment.—1. An irreversible coma developed after 500 units of insulin, although the patient had tolerated 2,000 units the previous day.

2. The electroencephalogram taken previous to treatments was abnormal.

3. After the last treatments the patient was lethargic, and on the night preceding the fatal treatment he was confused.

4. An increasing blood pressure and a decreasing pulse rate were observed during the protracted coma.

5. Sudden respiratory arrest occurred during intubation.

CASE 8.—*A white woman aged 53, with a diagnosis of manic-depressive psychosis, was treated with insulin subcoma. The therapy was conducted at home by general practitioners. Prolonged coma developed after an alleged dose of 120 units of insulin. She was admitted to a general hospital, where she remained disoriented and semicomatose for six weeks. She died after transfer to an institution. Autopsy revealed bronchopneumonia and encephalopathy, presumably due to hypoglycemia.*

The available facts indicate that over a period of about 10 years she had been repeatedly hospitalized with recurrent attacks of the psychosis. Treatment of the final psychiatric illness was undertaken by two general practitioners, who placed the patient on insulin subcoma therapy at home. After "numerous" such treatments, the number of which was unknown, she suffered a fall down a flight of steps. No known injuries occurred. Insulin therapy was continued. Seven

days later, after a dose of from 120 to 140 units of insulin, she lapsed into coma. She never regained full consciousness.

She was admitted to a general hospital with an inadequate history. Ventriculographic and encephalographic studies, lumbar punctures, roentgenographic studies of the skull, and hepatic function tests revealed nothing abnormal. Since the history of the previous insulin treatment was not known at this hospital, a diagnosis of hypothalamic lesion, probably vascular, was made. For the next six weeks she was in turn disoriented, overactive, and semicomatous. She had to be tube-fed and catheterized daily.

Shortly before death she was transferred to a psychiatric institution, where she died six hours after admission.

At autopsy the only gross lesion observed was bronchopneumonia. Microscopically, the brain showed diffuse and focal dropping out of neurones, general astrocytic gliosis, perivascular fibrosis, endothelial proliferation, and numerous "rod cells." A detailed report of this case will be published elsewhere.

Comment.—The patient received insulin subcoma therapy at home. Prolonged coma developed. It is concluded that insulin therapy at home may be hazardous.

TABLE 1.—*Summary of Circumstances of the Fatal Reactions*

Case	Circumstances	No. of Treatments	No. of Comas	Dose *
Group 1:	Sudden death before termination of an apparently routine coma			
1	Primary cardiac failure (?)	63	28	360
2	Primary respiratory failure (?)	11	3	700
Group 2:	Prolonged coma			
3	Continued coma for 41 hr.; anoxia	8	3	140
4	Unsuccessful termination; 15 min. later sudden death, following gastric intubation	12	3	450
5	Unsuccessful termination; 2 hr. later sudden death during laryngoscopic intubation	5	3	70
7	Unsuccessful termination; respiratory arrest 8 hr. later, during aspiration	10	2	500
Group 3:	Deaths following subcoma reactions			
6	Fatal "after-shock" following subcoma reaction; death in about 1 hr.; anoxia	54	18 †	340
8	Unexpected coma in an intended subcoma regimen; death in 6 wk	(?)	1 (?)	ca. 120

* Units of insulin administered at fatal treatment.

† The patient did not have a coma reaction prior to the fatal "after-shock," but had on previous days had 18 comas.

GENERAL COMMENT

Pertinent information about the circumstances of death is summarized in Table 1. On clinical grounds, it is convenient to divide the fatal reactions into three groups: (1) sudden death before termination; (2) prolonged comas in which termination cannot be effected, and (3) relapse into coma after apparent termination of a subcoma reaction.

In five cases (1, 2, 4, 5, and 7) there was almost instantaneous death from cardiac or respiratory failure. In three of these (cases 4, 5, and 7) this occurred during an intubation procedure. In Cases 1 and 2 there was a history of untoward reaction—respiratory arrest and syncope, respectively—with drug administration. It is known that a minor trauma may occasionally precipitate acute, fatal neurogenic shock.[2] This mechanism may explain the reaction in these patients.

2. Jetter, W. W.: Fatal Circulatory Failure Caused by Electric Shock Therapy, Arch. Neurol. & Psychiat. **51**:557 (June) 1944.

In four cases (3, 6, 7, and 8) intractable coma developed, followed by progressive anoxia. In Case 8 death was delayed six weeks. The pathological report on this case will be published later. Pathological examination was not done in Cases 1 to 7. The reader is referred to an extensive review of the pathological aspect of insulin-coma deaths by Ferraro and Jervis.[3]

All the patients had exhibited one or more atypical or noteworthy features prior to the day of the fatal reaction. It is true that in many uncomplicated cases some of these features appear, but some of them may be interpreted to point out factors of ominous significance. The features which the authors offer as worthy of attention are summarized in Table 2.

TABLE 2.—*Summary of Considerable Clinical Features*

A. Features which suggest an altered physiological state or a tendency to aberrant physiological responses
   1. Cardiac murmurs or arrhythmias (Cases 2, 5, 6, and 7)
   2. Head injury with prolonged hospitalization (Case 3)
   3. Electroencephalographic abnormalities (Cases 5 and 7)
   4. Previous untoward reactions with administration of drugs—respiratory arrest with curare (Case 1) and syncope with injection of corticotropin (Case 2)

B. Features which might influence mechanisms which resist or increase hypoglycemia
   1. Malnutrition (Cases 3 and 5) and avitaminosis (Case 3)
   2. Overactivity of sympathetic nervous system, already present or maintained by excessive fear of treatment (Cases 2 and 7)
   3. Intravenous injections of ether immediately preceding administration of insulin (Case 2)
   4. Interruption of treatment (Cases 1 and 2) or previous insulin treatment (Case 5)
   5. Administration of drugs, such as atropine (Cases 2, 4, and 5) or barbiturates (Cases 1, 4, 5, and 7 during coma)
   6. Repeated administration of high doses of insulin (Cases 2 and 7)

C. Features which indicate altered sensitivity to insulin
   1. Marked refractoriness to insulin, as indicated by high dose requirements or frequent failure of coma to occur (Cases 1, 2, 6, and 7)
   2. Marked sensitivity to insulin, either already present or developing during treatment, and manifested by the following:
      (*a*) Production of coma by very small doses of insulin (Case 5)
      (*b*) Coma of unusual depth (Case 5)
      (*c*) Slow response to termination of coma (Cases 5, 6, and 7)
      (*d*) Tendency to "after-shock" (Cases 4, 6, and 7 [?])
      (*e*) Abnormally low vital signs—body temperature, pulse rates, or blood pressure determinations (Cases 1, 3, 4, 5, and 6)

The occurrence of hypoglycemia coma is apparently the result of the relative activity of two groups of factors: (1) those favoring hypoglycemia, including insulin, hepatic disease, malnutrition, and parasympathetic activity, and (2) those resisting hypoglycemia or tending to homeostasis, such as pituitary-adrenal, thyroid, and sympathetic-adrenal activity. In this frame of reference some of the data may assume meaning.

Table 2 shows the wide range of doses that proved fatal. We have seen 1,600 units of insulin fail to produce coma, whereas another patient had coma after 10 units and another after 15 units of insulin. The absolute dose, then, is hardly a determinant, and sensitivity to insulin must be a relative state, dependent upon a physiological balance of the forces mentioned.

3. Ferraro, A., and Jervis, G. A.: Brain Pathology in 4 Cases of Schizophrenia Treated with Insulin, Psychiatric Quart. **13**:207, 1939.

In Cases 1 and 2 death came suddenly before termination of the coma. In both cases it was difficult to produce coma. In the first case, only 18 of 54 treatments resulted in a coma, whereas in the second case 700 to 800 units was required in all three comas. Both patients had experienced untoward reactions to previous medication. The second patient manifested signs of overactivity of the sympathetic nervous system. We recently saw prolonged apnea during coma in a patient who was highly refractory to insulin and who habitually manifested tachycardia, mild systolic hypertension, excessive diaphoresis, and intermittent exophthalmos. A similar patient had 2:1 heart block during coma. There may be a group of patients in whom sympathetic overactivity, resistiveness to insulin, and a proclivity to sudden cardiorespiratory collapse can be found.

It is probable that oversensitivity to insulin is shown by (1) production of coma by unusually small doses or rapidly decreasing insulin requirements on successive days; (2) overly deep coma, i. e., fourth- or rapid third-stage coma; (3) delayed response to termination, and (4) a tendency to return to coma after termination, i. e., "after-shock." In five cases (3, 4, 5, 6, and 7) one or more of these features were presented prior to the fatal treatment. In two of these cases (3 and 5) the patient was undernourished when treatment began. In Cases 3 and 5, 120 and 70 units, respectively, produced the final coma.

In three cases (4, 6, and 7) sensitivity to insulin, not previously present, may have developed during the course of treatment. In Case 4 the dose was maintained constant at 450 units. This dose, at first inadequate to produce coma, then led to two "after-shocks" and finally to fatal prolonged coma. In Case 7, 500 units of insulin proved fatal, although 2,000 units had been tolerated on the previous day. In Case 6 numerous "after-shocks" occurred. The last three were on successive days; the final one proved fatal. On this final day a dose of 450 units proved inadequate for about five hours to effect coma. Then, although 75 gm. of glucose had meanwhile been administered, the blood sugar fell to 14 mg. per 100 cc., and fatal coma occurred. Administration of 125 gm. more glucose failed to terminate it. In these three cases the mechanism resisting hypoglycemia may have "decompensated." Such a collapse may also have occurred in Case 8, in which coma unexpectedly resulted from a dose calculated to produce subcoma. Heiman [4] and Proctor and Easton [5] have expressed similar concepts.

In Case 1 sudden bradycardia preceded death. Pulse rates of 54 to 60 per minute were observed in Case 3 during the fourth treatment and in Case 4 on the day preceding the fatal reaction. In Case 5 bradycardia was present on the patient's admission. In Case 6 preinjection pulse rates of 60 to 64 per minute were frequent. Pulse rates of about 60 per minute during the course of insulin therapy have been seen in six other patients at this hospital. Five of these had, or later exhibited, complications: Two had a nonfatal prolonged coma; one went into deep comas, difficult to terminate, on 30 units of insulin; one had 2:1 heart block during coma, and another had auricular extrasystoles and an abnormally low glucose tolerance curve.

4. Heiman, M.: Blood Sugar During and After the Hypoglycemic Coma of Insulin Shock Therapy, with Special Reference to the "Aftershock," Am. J. Psychiat. **98**:863, 1942.

5. Proctor, L. D., and Easton, N. L.: An Unusual Case of Prolonged Coma in Hypoglycemic Shock Treatment, Am. J. Psychiat. **99**:203, 1942.

Three patients had a low preinjection rectal temperature on the day preceding death—97.0 to 97.4 F. in Case 2; 96.4 F. in Case 4, and 97.0 F. in Case 5. In Case 4 hypotension was also exhibited (80/50 mm. Hg).

In this connection, we determined the vital signs before injection each morning in 37 women and 30 men who completed 50 comas, each without serious complications. Blood pressure readings below 90/50 mm. Hg occurred in three women patients, but were uncommon. Only one patient, a man, had a mean pulse rate below 70 (67 ±7.2). In the other subjects pulse rates below 68 per minute were unusual. No preinjection rectal temperature lower than 97.2 F. was observed, and readings below 97.6 F. were rare. The low vital signs observed in these fatal cases, therefore, are considered significant and abnormal.

It is possible that vital signs are related to insulin requirements, indicating the hypoglycemia-resisting activity. The same systems which maintain vital signs resist hypoglycemia. In the study of the uncomplicated cases mentioned, we have found complex, but significant, correlations between the dose of insulin and vital-sign determinations. It is beyond the scope of this paper to discuss these relations. They will be published elsewhere. Observation of the vital signs may be of considerable value in prognosticating the untoward reactions that may occur during insulin therapy.

The first seven patients reported in this paper showed evidence of abnormalities in insulin sensitivity prior to the fatal treatment. Those who died suddenly during routine coma were previously resistive to insulin; most of those who had the usual type of protracted coma showed evidence of oversensitivity to insulin prior to the fatal reaction. Repeated high doses of insulin may exhaust mechanisms which should compensate for hypoglycemia. In two or three patients (4, 6, and 7 [?]) "after-shock" occurred on the day before the fatal treatment. We concur with the opinion of Spencer[6] that a subject having postcoma confusion should have his treatment discontinued for a few days. We also advise caution in treating patients who exhibit low vital signs prior to or during treatment.

Certain factors which affect the balance between hypoglycemic- and hyperglycemic-producing forces can be controlled by the physician. It is advisable to consider this balance before administering drugs which affect the autonomic nervous system, hepatic function, or metabolism. Emaciation, avitaminosis, excessive fears of treatment, and other factors should be considered in evaluating the insulin patient.

Recent papers, for instance that of Cohen,[7] have described insulin therapy at home. In Case 6 fatal "after-shock" followed a subcoma reaction, and in Case 8 protracted coma developed during subcoma therapy. Subcoma regimens are hazardous and require careful supervision and experience.

SUMMARY

Eight fatal cases of insulin therapy in psychiatric practice are presented. Factors which may contribute to the fatal outcome are discussed.

6. Spencer, A. M.: Post-Hypoglycaemic Encephalopathy in Sakel's Insulin Treatment, J. Ment. Sc. **94**:513, 1948.

7. Cohen, N.: Treatment of Mental Illness at Home by Small Doses of Insulin: Appraisal of Results in 12 Cases, New England J. Med. **235**:612, 1946.

The following considerations may be of value in anticipating adverse reactions: (1) a history of such atypical responsivity to medication as respiratory collapse or syncope; (2) factors adversely affecting the physiological systems regulating insulin-glucose relationships, such as malnutrition, avitaminosis, use of certain drugs, autonomic imbalance, and excessive fear of treatment; (3) undue resistiveness to insulin as manifested by high dose requirements or the occurrence of relatively few comas. This may be accompanied by overactivity of the sympathetic nervous system, excessive fear of treatment, and a tendency to sudden cardiorespiratory complications; (4) undue sensitivity to insulin as manifested by (*a*) low or rapidly decreasing dose requirements; (*b*) unusually deep coma; (*c*) difficulty in termination of coma; (*d*) a tendency to "after-shock," and (*e*), probably, the presence of low vital signs.

MYOCLONUS OF MUSCLES OF THE EYE, FACE, AND THROAT

MORRIS B. BENDER, M.D.
MORTON NATHANSON, M.D.
AND
GUSTAVE G. GORDON, M.D.
NEW YORK

CASES of palatal myoclonus, sometimes known as palatal "nystagmus," have been described since 1886.[1] The disorder is defined as constant rhythmic movements of the palate and pharynx, varying in rate and amplitude, the rate being between 50 and 180 per minute. The movements may be synchronous with those of other organs, such as the larynx, eyeballs, and diaphragm.[2] Once a patient has acquired this disorder, the movements continue inexorably until death, although in some patients the movements may be halted during voluntary innervation, such as phonation and swallowing. The movements continue unchanged during sleep, respiratory and cardiac dysrhythmias, and general and local anesthesia.

The myoclonic movements involve the palate most commonly, and the pharynx, larynx, eyeballs, corner and floor of the mouth, and diaphragm, in that order of frequency. The intercostal muscles and extremities have been reported to be affected in rare instances.[3]

The palatal movements are quick, oscillatory contractions, consisting of a rapid elevation of the soft palate, followed immediately by a slightly slower depression. The faucial pillars approach each other toward the midline during the phase of elevation of the soft palate. The pharyngeal wall moves to and fro as the soft palate is elevated and depressed. Bilateral palatopharyngeal myoclonus is the

This work was aided (in part) by a Grant-in-Aid from the National Multiple Sclerosis Society.

From the Departments of Neurology and Psychiatry, New York University College of Medicine and Bellevue and Goldwater Memorial Hospitals, and the Neurologic Service of the Mount Sinai Hospital.

1. Spencer, H. R.: Pharyngeal and Laryngeal "Nystagmus," Lancet **2**:702, 1886.

2. Alajouanine, T.; Thurel, R., and Wolfrom, R.: Myoclonies rythmées du voile, de la glotte et du diaphragme, survenant par accès périodiques et se traduisant par du hoquet, Rev. neurol. **76**:96, 1944. Dobson, J. P., and Riley, H. A.: Rhythmic Myoclonus: A Clinical Report of Six Cases, Arch. Neurol. & Psychiat. **45**:145 (Jan.) 1941. Gallet, J.: Le nystagmus du voile, Thesis, Paris, 1927. Leshin, N., and Stone, T.: Continuous Rhythmic Movements of the Palate, Pharynx and Larynx, Arch. Neurol. & Psychiat. **26**:1236 (Dec.) 1931. Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Pharynx, Larynx and Other Regions: Clinical Report of Three Cases, ibid. **29**:726 (April) 1933.

3. Garcin, R.; Chavany, J. A., and Kipfer, M.: Sur le cas de deux sœurs atteintes l'une de myoclonie isolée du voile du palais, l'autre de mouvements oscillatoires rythmés des orteils, Rev. neurol. **77**:35, 1945. Lhermitte, J., and Sigwald, J.: Myoclonies rythmées du voile, du pharynx, du larynx et du membre supérieur gauche au cours d'un syndrome latéral du bulbe, ibid. **73**:81, 1941.

common finding, although unilateral movements have been described in six cases. The laryngeal movements can be seen and palpated in the neck as oscillatory elevations and depressions of the larynx. The best methods are by direct and indirect laryngoscopy. Fluoroscopy is used to observe the myoclonic movements of the diaphragm.[4] Occasionally a fluttering movement can be seen in the epigastrium with the patient in a semirecumbent position. When movements of the eyeballs are present, they appear as gross, rhythmic, and jerky. They may be observed in any direction of gaze, and often they are synchronous with other myoclonic movements, particularly of the face. The facial movements are most apparent about the corners of the mouth.

The patient is usually not conscious of palatal or other concurrent myoclonic movements. Surprisingly enough, they do not interfere with swallowing, talking, or respiration. Frequently the patient is aware of a "clicking" sound in his ears, presumably due to the contractions of the tensor veli palatini muscles. This clicking noise may be audible to the examiner.

The object of the present communication is to present observations made on eight patients who showed rhythmic movements of the palate and other structures. In three of these patients we studied the effect of amobarbital sodium (sodium amytal®) and mephenesin (tolserol®) on the rate and character of the myoclonic movements of the palate and in one of the eyes. In one of these patients the ocular, facial, and laryngeal movements were electrically recorded. Studies were made as to the relation of the palatal movements with movements of the larynx, eyeballs, and diaphragm and with the pulse and respiration rates. In another case we determined the approximate anatomic site of the lesions through roentgenograms and the surgeon's report at operation for removal of a foreign body. In still another case we obtained a postmortem examination, so that we have detailed anatomic data on the brain. Observations on myoclonic movements during electrical stimulation of the brain stem in monkeys also are presented.

CLINICAL STUDIES

Case 1.—J. M., a chronic alcoholic, aged 69, was admitted to the Goldwater Memorial Hospital because of recurring episodes of gouty pain in the right big toe for 23 years. He had had a tremor of both hands for 30 years. Six months prior to admission he had a sudden episode of sweating and vomiting, followed by inability to speak and weakness of the right arm. Subsequently the speech difficulty and weakness improved.

On examination the patient was euphoric and garrulous. The blood pressure was 200 systolic and 100 diastolic. The speech was dysarthric. There was slight weakness of the right lower facial muscles.

There were myoclonic movements of the right lower facial muscles and throat. These movements were grossly apparent on inspection and palpation. The facial movements consisted of fine, tremor-like oscillations. The movements of the throat were seen as rhythmic elevations, most conspicuous over the thyroid area and resembling the pulsating movements of the carotid arteries. Examination of the pharynx revealed myoclonic movements of both sides of the palate, the base of the tongue, and the posterior pharynx. All these myoclonic movements were continuous rhythmic, and synchronous. The rate was 140 per minute. The movements were not abolished when the patient continuously phonated the sound "ah."

The tendon reflexes were slightly hyperactive on the right side. Pathologic reflexes were not elicited. There were some atrophy and weakness of the right interosseus muscles. There

4. Thibonneau, M.: Myoclonus du diaphragme, J. radiol. et d'electrol. **25**:143, 1942-1943.

was tremor of the left upper extremity with dysmetria and lack of stabilization in the finger-to-nose test. The tremors were not synchronous with the palatal movements. The neurologic status was otherwise normal. The results of laboratory tests were normal.

The clinical diagnosis was cerebral arteriosclerosis, affecting the vessels of the brain stem, and hypertensive cardiovascular disease.

Case 2.—F. K., a man aged 58, had complained of episodes of headache, dizziness, blurring of vision, and staggering gait for one year prior to his admission to the medical service of the Goldwater Memorial Hospital.

On examination, the patient presented a picture of severe mental confusion. The blood pressure was 240 systolic and 125 diastolic. The heart was enlarged to the left. The fundi revealed retinopathy, moderate swelling of the optic disk margins, and small patches of hemorrhage and exudate.

Palatal and pharyngeal myoclonic movements were observed on inspection of the throat. These consisted of symmetrical, gross, jerky movements of both faucial pillars upward and toward each other in the midline. The posterior and lateral pharyngeal walls contracted synchronously with the elevations of the faucial pillars, at the rate of 120 per minute. However, on phonation, when the patient was asked to say "ah," the movements temporarily halted but were resumed immediately upon cessation of the phonation.

The tendon reflexes of the left extremities were more active than those on the right. The abdominal reflexes were absent. The gait revealed trunkal asynergia with lurching to the right. There were a tremor of the head and an intention tremor and dysdiadokokinesis in the right upper extremity. However, these tremors were not synchronous with the myoclonic movements.

The spinal fluid findings were normal. Examination of the kidneys showed renal impairment in both the concentration and the phenolsulfonphthalein test. An electrocardiogram revealed a hypertensive pattern.

The patient's mental condition gradually deteriorated; the renal insufficiency increased, and the patient died in uremia one year after admission. Throughout this period the myoclonic movements of the palate and pharynx continued unchanged. Necropsy was not performed. The diagnosis was diffuse arteriosclerosis of the central nervous system, involving the cerebrum, cerebellum, and brain stem.

Case 3.—G. K., a man aged 56, was admitted to the Goldwater Memorial Hospital because of dyspnea. He had a paretic left lower extremity as a result of poliomyelitis in childhood. Four years prior to admission he had had a cerebral accident, characterized by a sudden onset of unconsciousness, which lasted only a few minutes, and slight weakness of the left upper extremity, which improved rapidly. Two years before admission he noticed unsteadiness and "shaking" of the left arm and occasional twitching of the left shoulder.

The blood pressure was 220 systolic and 120 diastolic. There was pronounced sclerosis of the peripheral arteries of the extremities.

Examination of the pharynx revealed fine, rhythmic, continuous myoclonic movements of the right faucial pillar, at the rate of 130 per minute. There were no movements of the left side of the palate. The movements were not suppressed by phonation.

There was slight paresis of the left upper extremity with hypoactive tendon reflexes. The left lower extremity was paretic and atrophic, with absence of tendon reflexes. There were a marked intension tremor and dysmetria on finger-to-nose testing of the left upper extremity. There was no tremor at rest.

The diagnosis was hypertensive heart disease and arteriosclerosis involving the brain stem.

Case 4.—R. P., a man aged 52, gave a history of vertigo, progressive weakness of both legs, and increasing unsteadiness of gait for two years before his admission to the Goldwater Memorial Hospital. He had had an untreated penile chancre 25 years prior to hospitalization.

On examination the heart was observed to be enlarged to the left. There was a diastolic murmur over the aorta. The blood pressure was 138 systolic and 108 diastolic. Psychiatrically, the patient showed confusion and other symptoms of dementia. The pupils were equal and reacted sluggishly to light and in accommodation. Visual acuity was markedly impaired in both eyes. The fundi showed severe arteriosclerotic changes. There was bilateral internal strabismus.

The speech was nasal. Slight weakness of the right lower part of the face was present. Examination of the pharynx revealed constant, rhythmic, myoclonic movements of both sides

of the palate and oropharynx, at the rate of 130 per minute. The movements were visible in the neck as pulsating movements of the laryngeal area. The movements were not abolished by phonation.

The gait was ataxic. There were marked dysmetria and clumsiness on finger-to-nose and heel-to-knee testing of each side.

The Wassermann reaction of the blood was 4+, but the spinal fluid was normal. The electrocardiogram showed a left axis deviation. A roentgenogram of the chest revealed slight widening of the aorta.

The diagnosis was syphilitic aortitis and diffuse arteriosclerosis of the cerebrum, cerebellum, and brain stem.

CASE 5.—S. M., a man aged 73, gave a history of sudden onset of weakness and pain of the left lower extremity in June, 1946. There was no loss of consciousness. Six months later he was admitted to the Queens General Hospital for investigation of the pain in the left leg, which had persisted for several months. There it was noted that the patient was hoarse and had paralysis of the right vocal cord. After three months the pain in the leg subsided, and he was transferred to the Goldwater Memorial Hospital for further care. Because of language difficulty, it could never be ascertained when the patient's hoarseness first appeared.

Examination revealed that the heart was enlarged to the left. The blood pressure was 190 systolic and 100 diastolic. There was a small epithelioma of the forehead. The patient was irritable and retarded in responding to commands and exhibited episodes of unmotivated crying and laughter.

Examination of the throat showed constant, rhythmic myoclonic movements of both sides of the palate and the oropharynx, at the rate of 140 per minute. The movements were not suppressed during phonation. The movements were not visible in the neck. The right vocal cord was adducted and paretic. There was no swallowing difficulty. The voice was hoarse; the speech was slurred and dysarthric. The tongue was in the midline and showed no atrophies. The uvula was in the midline. The gag reflex was absent on both sides.

The gait was broad-based, unsteady, and lurching. There was moderate dysmetria on finger-to-nose and heel-to-knee testing on both sides.

The epithelioma of the forehead was easily removed surgically. Pathologic examination of the growth revealed it to be a basal-cell carcinoma. No recurrence or metastasis of the tumor has appeared to date, six months after surgical removal. The neurologic status remains unchanged.

The diagnosis was arteriosclerosis of the brain stem, hypertensive cardiovascular disease, and basal-cell carcinoma on the right side of the forehead.

CASE 6.—R. M., a man aged 59, gave a four-year history of hypertension and cardiac decompensation, with several cerebral accidents. In one of them he had right hemiparesis, which has persisted. Six months prior to admission to the Goldwater Memorial Hospital he had a sudden episode of difficulty in swallowing, slurred speech, and tingling and weakness of the right arm and leg.

Examination showed an enlarged heart and a blood pressure of 200 systolic and 100 diastolic. The patient had frequent outbursts of unprovoked crying and laughing. The pupils were irregular and unequal and reacted sluggishly to light and in accommodation. The gait was reeling. There were dysdiadokokinesis and dysmetria on finger-to-nose testing on the left side. There was right hemiparesis, with concomitant hyperreflexia and a Babinski sign.

Six months after admission, the patient had another cerebral accident, accompanied with difficulty in swallowing and slurred speech. It was then noted that there were constant, rhythmic, myoclonic movements of both sides of the palate, oropharynx, and larynx. All these movements were synchronous, at the rate of 130 per minute. The palatal movements were not suppressed on phonation. Several months later rhythmic movements of both eyeballs, synchronous with the palatal movements, were also noted. The eye movements consisted of gross rolling of both eyeballs, which moved synchronously, although the excursions of the right eye were of greater amplitude and more rotary than those of the left. These movements varied with fixation of gaze. When the patient fixed on an object, the rhythmic eye movements, although present, were barely perceptible. However, when the patient closed his eyes, either voluntarily or in sleep, the movements became conspicuous. When the eye movements were first noted by the examiner,

the patient complained of double vision, which was present on lateral gaze to either side and was still present when the patient closed either eye. There was no complaint of abnormal movement of objects in the visual field. No weakness of the eye muscles was noted at any time. The complaint of double vision disappeared after several weeks, although the spontaneous rhythmic movements of the eyeballs have continued. There were also rapid, jerking movements of the diaphragm. However, even under fluoroscopic observation, it was difficult to determine whether these diaphragmatic movements were synchronous with the palatal movements.

About six months later, or approximately one year after the palatal movements were first noted, synchronous myoclonic movements of the right lower facial musculature appeared. At this time, on Aug. 12, the following observations were made: The patient appeared dyspneic. Speech was nasal and dysarthric. There were rhythmic movements in the epiglottis, at the rate of about two per second. Associated with these were movements of the palate, tongue, both corners of the mouth, both sides of the diaphragm, and both eyes and eyelids. The eye move-

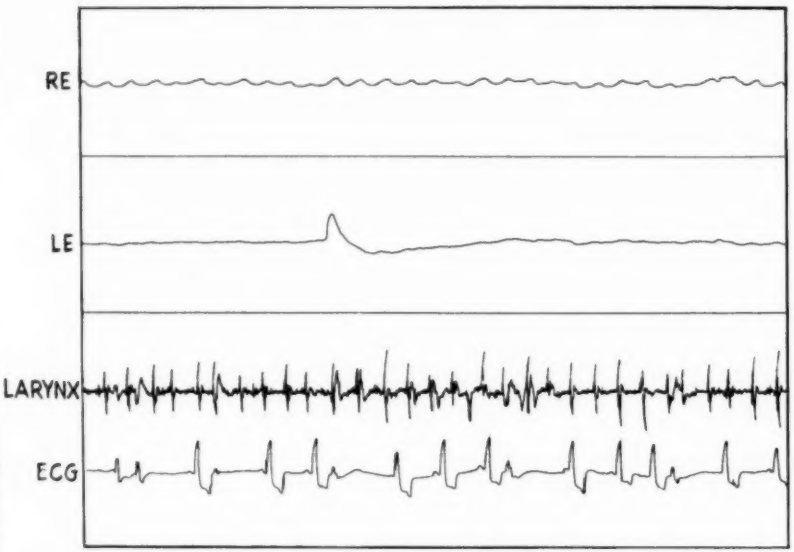

Fig. 1 (Case 6).—Simultaneous electrical recording from the eyes, larynx, and heart beat. This record shows the synchrony of the movements of the eyes and larynx, as compared with the slower, irregular heart beat. Note that the myoclonic movements of the right eye are much more apparent than those of the left eye. Except for one artifact, the electrical corneoretinal record from the left eye is practically flat.

ments on direct forward gaze were rotatory, showing a clockwise twist. On right lateral gaze the clockwise rotatory ocular movements became more pronounced. On left lateral gaze there was nystagmus with a clockwise component. On upward gaze there were rotatory clockwise ocular movements, more pronounced in the right eye. The same was true on downward gaze and on direct forward gaze. With the eyes closed, the globes were seen to move back and forth in the horizontal plane with a rotatory clockwise component. These movements were quite prominent. The eyelids moved synchronously with the globes. When the eyes were closed tightly, both globes tended to deviate to the left and slightly upward. At the same time, the rhythmic clockwise torsion movements of the eyes persisted.

The rhythmic movements described were not directly related to the rhythm of the pulse or to that of respiration. This was shown by simultaneous electrical recording from the eye, face, larynx, and pulse (Figs. 1 and 2).

There were also movements of the anus and perianal area. These, however, appeared to be synchronous with the irregular diaphragmatic movements. There appeared to be no relation between the anal and the palatal or other spontaneous rhythmic movements.

Effect of Amobarbital Sodium.—It is known that intravenous injections of amobarbital will abolish nystagmus which is present on direct forward gaze. For this reason, we thought that this drug might have a similar effect on the palatal myoclonus.[5] This prediction was not borne out. Under amobarbital sodium narcosis, all the myoclonic movements persisted. Only the rhythmic ocular movements were abolished. Neither the lids nor the eyeballs moved when the eyes were open or closed under barbiturate narcosis. This abolition of eye and lid movements appeared within two minutes after 0.23 gm. of amobarbital sodium was given intravenously. This

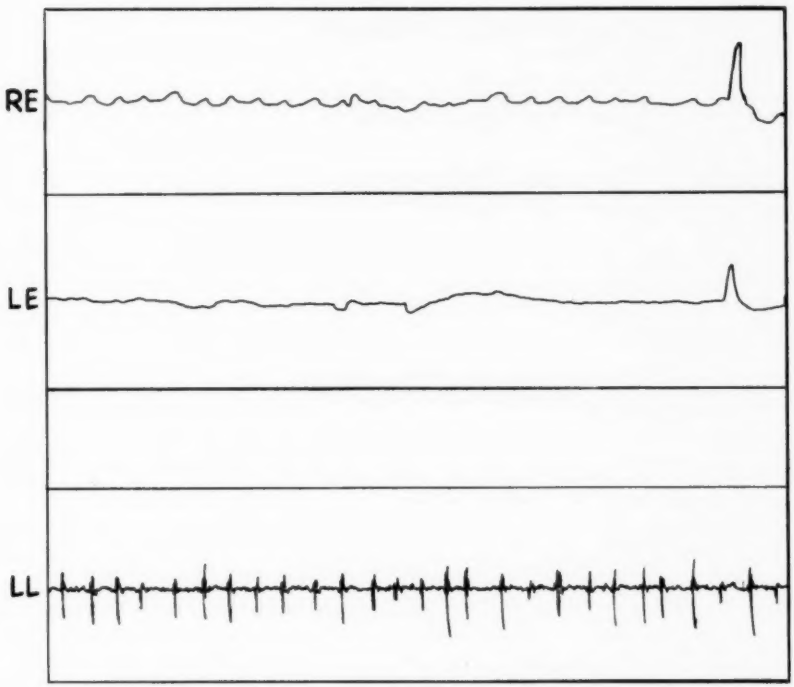

Fig. 2 (Case 6).—Simultaneous electrical recording of the eyes and the lower lip (*LL*). This shows synchrony between the eye and the lip movements. Again, the movements of the right eye are greater than those of the left eye.

effect persisted for 30 minutes. It should be noted that during this period coarse nystagmus was apparent when the eyes turned in any direction. At no time were the palatal, laryngeal, facial, or diaphragmatic movements abolished or reduced. There was no effect even when the patient was extremely drowsy and did not respond to questions.

5. Bender, M. B.: Effects of Barbiturates on Ocular Movements (Nystagmus), Confinia neurol. **7**:144, 1946. Bender, M. B., and O'Brien, F. H.: The Influence of Barbiturate on Various Forms of Nystagmus, Am. J. Ophth. **29**:1541, 1946. Bender, M. B.; Nathanson, M., and Green, M.: Effects of Intravenous Tolserol on Normal and Abnormal Eye Movements (Nystagmus), ibid. **34**:579, 1951.

The patient was given 100% pure oxygen by means of an anesthesia mask for 15 minutes. Neither the palatal nor the ocular movements were altered. It was interesting that the patient was unaware of the ocular or palatal movements, even though the movements of the throat were gross enough that they could be easily observed from a distance of several feet. The movements have continued at the same rate during the entire two-year period that the patient has been under observation for this phenomenon.

The Wassermann reaction of the blood was positive. Lumbar puncture revealed a clear and colorless fluid under an initial pressure of 100 mm. of water. During the manometric readings irregular fluctuations in pressure of up to 200 mm. were apparent. These fluctuations were not synchronous with the palatal rhythm. The spinal fluid contained 10 lymphocytes per cubic millimeter, 87 mg. of protein per 100 cc., a colloidal gold curve of 123344320, and a negative Wassermann reaction.

The diagnosis was hypertensive cardiovascular disease, syphilitic aortitis, aortic insufficiency, and diffuse cerebral arteriosclerosis.

Case 7.—C. W., a disabled veteran of World War II, aged 30, was seen by us on March 23, 1949. Since then this case has been reported by Jacobson and Gorman.[6] Abnormal movements of the palate, pharynx, and epiglottis were noted. A detailed record of his injury, operations, and clinical findings was obtained from the files of the Veterans Administration.

In December, 1943, the patient sustained an injury to the left mastoid region while in combat. A small "foreign body" was removed. He was well again until September 12, 1944, when he was injured by a shell fragment which penetrated the right temporoparietal region of the head. On regaining consciousness, 11 days after the injury, the patient was found to have slurred speech, dysarthria, left homonymous hemianopsia, and ataxia of all extremities. A roentgenogram of the skull showed a large, ragged metallic foreign body in the left posterior fossa. This subsequently proved to be in the left cerebellar hemisphere. During the next 18 months no change in the neurologic status was noted. However, it was reported that he had had two generalized convulsions. The dysarthria and the ataxia of the four limbs persisted. On Feb. 15, 1946, the foreign body was found to be lodged in the left cerebellar hemisphere. "A transverse incision was made along the line of the cerebellar folia. With the suction tube the tissue around the foreign body was aspirated, and the body was then dislodged and removed. The entire procedure was carried out with local infiltration, and without any complaints from the patient."

On March 18, 1946, abnormal movements of the palate were noted for the first time. These were observed by Dr. F. A. Quadfasel, who described them as follows: "Myoclonus involves the palate, pillar, and posterior wall. The palate moves slightly to the left and downward. The posterior wall and pillar to the midline of the tongue on the left is lifted passively with each contraction. The frequency is about 30 contractions per minute. No contraction was observed in the muscles of the eye or of the chest wall."[7]

In May, 1946, "a Jacksonian attack involving the left side of the face" was noted. On Jan. 22, 1947, the following neurologic findings were noted: There was nystagmus on lateral gaze to either side. At that time the patient was receiving barbiturates. A left homonymous hemianopsia was demonstrated. The soft palate was drawn up to the left and moved rhythmically from side to side. These movements were synchronous with fine movements of the lower lip, chin, and platysma muscle bilaterally. Speech was described as monotonous, slow, and of cerebellar type. There were ataxia of the four limbs and adiadokokinesis of the upper extremities.

Our examination in May, 1949, disclosed a similar condition, namely, left homonymous hemianopsia, nystagmus on direct forward gaze, and rhythmic myoclonic movements of the palate, pharynx, epiglottis, and larynx. These movements were continuous and were not abolished by phonation. The speech was slow, syllabic, and nasal in quality. There was bilateral adiadokokinesis, more pronounced on the left, and the patient was unable to walk because of marked bilateral ataxia. The status was otherwise normal.

6. Jacobson, M. B., and Gorman, W. F.: Palatal Myoclonus and Primary Nystagmus Following Trauma, Arch. Neurol. & Psychiat. **62**:798-801 (Dec.) 1949.

7. It is possible that the myoclonus was there before, but since the patient had not been examined previously by a competent neurologist, this is not known.

Special Tests.—Stimulation of the carotid sinus, pressure on the eyeball, and voluntary breath holding did not alter the nature of the myoclonic movements. Fluoroscopic examination revealed normal excursions of the diaphragm. Caloric stimulation of the ear produced normal ocular responses but had no effect on the palatal myoclonus.

Immediately after the injection of 0.25 gm. of amobarbital sodium, over a period of two and one-half minutes, the nystagmus on direct forward gaze ceased and did not reappear until 1½ hours thereafter. The myoclonus of the palate, larynx, and facial muscles continued, without change in frequency or character.

CASE 8.—R. W., a man aged 22, was admitted with a history of sudden onset of headache, nausea, and vomiting on Oct. 2, 1949. One week later he complained of transient diplopia, and on the following morning there was weakness of the right side of the face. On admission to the Mount Sinai Hospital on Nov. 6, 1948, he showed paralysis of the right side of the face of peripheral type, weakness of conjugate ocular gaze to the right, ataxia of the right extremities, and decreased auditory acuity on the right. Caloric tests with cold water revealed a nonfunctioning labyrinth on the right. While the patient was under observation there developed weakness of the right lateral rectus muscle and diplopia on central gaze. Within three weeks there was improvement. The paresis of right conjugate gaze, the weakness of the right lateral rectus, and the right facial paresis disappeared almost completely, while the ataxia of the right extremities lessened. The cerebrospinal fluid showed 8 lymphocytes per cubic millimeter and a total protein of 88 mg. per 100 cc. The impression was that the patient had acute encephalitis, but the possibility of multiple sclerosis was considered.

Several days after his discharge from the Mount Sinai Hospital there was a sudden onset of weakness of the left side of the face, which disappeared within one week. During the following six months the patient was relatively asymptomatic except for an occasional episode of double vision and the persistent, but slight, ataxia of the right upper and lower extremities.

In the middle of September, 1949, he began to complain of numbness and weakness of both feet, and within the next five days there developed complete paralysis of the lower extremities, with vesical and rectal incontinence.

The past history revealed that from the ages of 9 to 12 the patient's left lower extremity was in a cast because of suspected "tuberculosis" of the left knee joint. Since the age of 14 he had had a nonproductive cough. In 1945 he was rejected by the draft board because of a "suspicious chest x-ray." During the next two years repeated examinations of the sputum and x-ray examinations of the chest showed no evidence of tuberculosis. He was told he had "unresolved pneumonia."

The general physical examination on his admission to Bellevue Hospital revealed essentially nothing abnormal except for an indurated area, approximately 3 to 5 cm., just to the right of the midthoracic portion of the spine.

The neurologic examination on admission disclosed a coarse, rapid nystagmus in all directions of gaze and in central fixation. The nystagmus on direct forward gaze was in the vertical plane. The patient complained of objects bobbing "up and down" on central fixation at a far point (oscillopsia). Slight ataxia of the right upper extremity was noted. There were flaccid paraplegia, absence of the left knee jerk, and depression of the other tendon reflexes. A well-demarcated sensory defect for all modalities was evident below the level of the seventh thoracic spinal segment.

There were rhythmic, continuous movements of the right side of the palate and pharynx, at a rate of 130 per minute. Slight movement of the right side of the palate and pharynx toward the left was also noted. The right posterior pharyngeal wall moved to and fro, and the right side of the palate and the right faucial pillar moved synchronously from side to side. Phonation did not affect the movements. The larynx and diaphragm were not involved. The palatopharyngeal movements showed no synchrony with the nystagmus on direct forward gaze or with the pulse rate. The palatal movements persisted during sleep. The patient denied awareness of the movements, and the examiner could not detect audible "clicking" at close range. The right palatopharyngeal myoclonic movements persisted without change in character until death.

Effect of Amobarbital Sodium and Mephenesin on Rhythmic Movements of the Palate and Eyeballs.—Intravenous injection of amobarbital sodium failed to alter the rate and amplitude of the palatal and pharyngeal movements. On the other hand, it abolished the oscillopsia and

nystagmus on forward gaze and enhanced the nystagmus on lateral and vertical gaze. Approximately 5 grains (0.324 gm.) of amobarbital sodium was injected intravenously within four minutes. Three minutes after the injection was started the nystagmus on direct forward gaze and the oscillopsia disappeared. Five minutes later there was no response to stimulation with the opticomotor drum. The lack of opticomotor response persisted for nine minutes. Twenty minutes after the injection was started the nystagmus on direct forward gaze returned, but it was not accompanied by the return of the oscillopsia until approximately 15 minutes later. During the entire observation period there was shimmering nystagmus on horizontal gaze to either side. There was no alteration of the palatal myoclonus.

Intravenous injections of mephenesin produced almost the same effects as amobarbital sodium. Fifty cubic centimeters of 2% mephenesin was given intravenously in one minute. Six minutes later the nystagmus on direct forward gaze and the oscillopsia had disappeared. Lack of response to the opticomotor drum was noted at 13 minutes. This effect lasted 12 minutes. The nystagmus on direct forward gaze returned in 28 minutes, but the cessation of the oscillopsia persisted for an additional 70 minutes. During this entire period of observation following the injection of the drug the nystagmus present on ocular deviation became very rapid, almost shimmering in character. The drug had no significant effect on the palatal myoclonus.

Caloric stimulations of each auditory canal with cold water failed to produce visible changes in the character and rate of the ocular nystagmus. There was no vertigo or nausea. The palatopharyngeal myoclonus was not affected by the caloric stimulations.

Spinal puncture shortly after admission disclosed xanthochromic spinal fluid, containing 200 red blood cells per cubic millimeter. The total protein was 864 mg. per 100 cc. Only a small amount of fluid could be obtained, and adequate manometric tests were impossible. A cisternal myelogram showed a complete block of the ethyl iodophenylundecylate (pantopaque®) at the level of the sixth dorsal vertebra; the cisternal fluid was clear and colorless, and the total protein was 39 mg. per 100 cc. Roentgenograms of the chest taken in the supine position showed obliteration of the left lateral costophrenic sulcus by "thickened pleura or minimal effusion." The thoracic, lumbar, and sacral roentgenograms appeared normal except for "suggestive inflammatory changes" involving the left eighth rib at its vertebral extremity. All other pertinent laboratory findings were normal.

The subcutaneous mass to the left of the spine in the midthoracic region was noted to be larger and more indurated than it was on admission. A biopsy diagnosis of this tissue was reported as reticulum cell sarcoma. A laminectomy was performed, and similar tumor tissue was subsequently located in the extradural and intradural regions at the level of the fifth to the eighth thoracic vertebrae. On opening the dura, it was noted that the spinal cord was congested, discolored, and swollen. After the laminectomy the course was downhill, and the patient died on Jan. 16, 1950, at the Meadowbrook Hospital, Hempstead, N. Y. The neurologic status during this period was essentially unchanged. Several hours prior to his death, when the patient was semistuporous, it was noted that the palatopharyngeal myoclonus was present and exhibited the same character and rate as on previous examinations.

B. PATHOLOGIC STUDY (CASE 8)

Autopsy was performed by Dr. Theodore J. Curphey, Chief Pathologist at the Meadowbrook Hospital. Special examinations of the brain were made under the direction of Dr. Lewis Stevenson, Neuropathologist, Bellevue Hospital.

The brain weighed 1,200 gm. The dura showed an irregular, grayish, elevated, indurated area, approximately 2 by 3 cm., on the inner surface of the right parieto-occipital region. Cut sections showed that tumor tissue infiltrated the entire thickness of the dura. The sagittal sinus was patent. The cerebral hemispheres were symmetrical. There were no areas of softening. The arachnoid membranes were slightly opaque. No abnormalities of the gyri, sulci, or vessels on the surface of the brain were noted. On section of the cerebrum, cerebellum, and brain stem no gross abnormalities were detected.

The dura of the spinal cord was thick and adherent to the midthoracic region. It presented indurated, light grayish, raised, irregular areas. Section through this area showed tumor tissue infiltrating the entire dura, the arachnoid, and the posterior aspect of the cord.

Tumor tissue was also noted in the lungs, kidneys, testes, and liver. These organs presented irregular, large and small, grayish, indurated areas.

Fig. 3.—Demyelination of the left inferior olivary, right restiform body, and right dentate nucleus. The left inferior olivary appears larger than the right. Myelin-sheath stain; × 2½.

Fig. 4.—Demyelination in the region of the right dentate nucleus and rostral portion of the right restiform body. Myelin-sheath stain; × 2½.

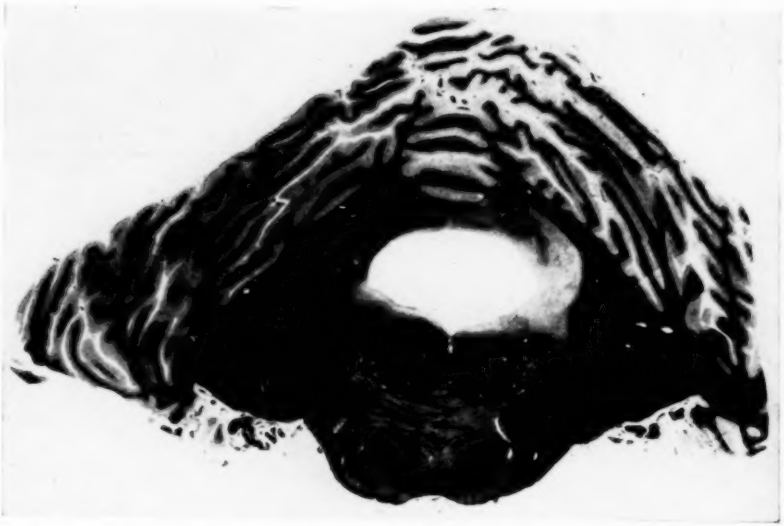

Fig. 5.—Demyelination in the region of the right dentate nucleus at a more rostral level. Myelin-sheath stain; × 2½.

Fig. 6.—Partial demyelination of the right superior cerebellar peduncle. Myelin-sheath stain; × 2½.

Microscopic examination of serial sections of the entire brain stem disclosed conspicuous changes in the left inferior olivary nucleus, the right dentate nucleus, and the right restiform body (inferior cerebellar peduncle). These can be seen with the naked eye in Figure 3. The myelin-sheath stain revealed distinct demyelination in the regions cited, particularly the right inferior and superior cerebellar peduncles (Figs. 4, 5 and 6). In addition, the left inferior olivary nucleus appeared larger than the right. There was also slight demyelination in the hilus of the right inferior olivary nucleus (Fig. 7).

Nissl, cresyl violet, and hematoxylin-eosin stains showed a decrease in the number of ganglion cells within the left inferior olivary nucleus; rarefaction, congestion, and small hemorrhages in the region of the right dentate nucleus; gliosis in this region, and a distinct decrease in the number of Purkinje cells in the right half of the cerebellum. There was round-cell infiltration, particularly in the region of the right dentate nucleus. Sections through the rest of the brain stem did not reveal any abnormalities.

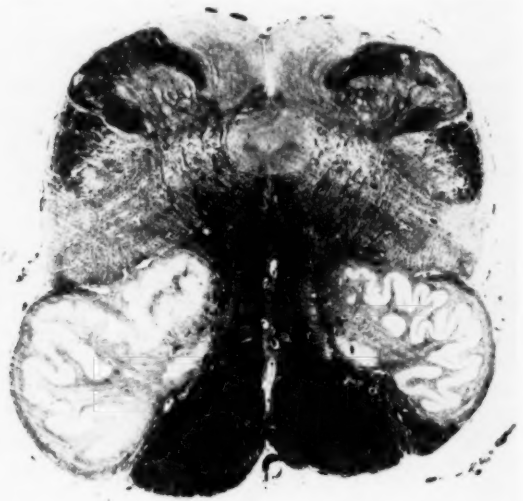

Fig. 7.—Apparent hypertrophy of the left inferior olivary. There is also striking demyelination of the fibers within the left and some within the right inferior olivary. Myelin-sheath stain; × 7.

COMMENT

Comment.—More than 100 cases of rhythmic myoclonus of the palate and pharynx have been reported in the literature. In some of these cases an autopsy was performed. The commonest cause of this disorder is cerebral arteriosclerosis, but tumors, multiple sclerosis, and, rarely, encephalitis may be etiological factors.

Urechia and associates[8] reported two cases of what they called congenital rhythmic myoclonus. However, from their description it appears that the cases do not belong to the clinical syndrome under discussion. There were no rhythmic movements of the palate, pharynx, and larynx, and in one of the cases the movements disappeared completely when the patient was at rest. Trauma as a cause

8. Urechia, C. I.; Dragomir, L., and Rosu, S.: Sur deux cas de myoclonies rythmiques congenitals, Monatsschr. Psychiat. u. Neurol. **106**:263, 1942.

was described by Belman,[9] and more recently by Jacobson and Gorman.[6] Baruk and associates[11] described a case of palatal myoclonus following electric shock.

The pathologic picture of this disorder has been clarified by numerous authors.[12] In general, it was found that palatal myoclonus was associated with lesions involving the inferior olivary nucleus or the central tegmental fasciculus. However, lesions have also been observed along the various pathways which connect the inferior olivary nucleus with the dentate nucleus and the red nucleus. A striking finding in examination of the brain is pseudohypertrophy or swelling of the inferior olivary nucleus. The pathologic changes in the olivary nucleus consist of swelling of the nerve cells, thickening of their processes, displacement of the nuclei, and vacuolization. There is increased neuroglia formation in and around the olivary nucleus. In general, the lesions involve the brain stem and the cerebellum, more particularly the triangle formed by the inferior olivary nucleus, the red nucleus, and the dentate nucleus. Usually these structural changes are bilateral, and in these instances the myoclonus is bilateral. In our own case, both the symptoms and the pathologic changes showed "sidedness." Right palatal myoclonus was correlated with lesions in the left inferior olivary nucleus, right dentate nucleus, and right inferior and superior cerebellar peduncles. One might ask whether this combination of lesions is necessary for the appearance of the symptoms. This question is difficult to answer from our clinicopathologic studies. However, observations made on the experimental animal may give at least a part of the answer.

EXPERIMENTAL STUDY

Exploration of the brain stem of the monkey with the aid of the Horsley-Clarke instrument revealed that electrical stimulation of certain regions in the brain stem produced palatal myoclonus.[13] The specific regions stimulated were situated in the reticular substance, just dorsal and medial to the inferior olivary nucleus, and also within the dorsal and medial regions of the olivary nucleus itself. The palatal myoclonus thus elicited was ipsilateral, and at times bilateral. Stimulation with a thyratron stimulator, using double-needle electrodes, the total diameter of which

9. Belman, E. D.: Traumatic Velopalatine Myoclonus, Nevropat. i psikhiat. **16**:43, 1947.

10. Footnote deleted.

11. Baruk, H.; Osianik, and Borenstein: Myoclonies vélo-palato-laryngées consécutives a l'électro-choc: Remarques critiques sur cette méthode thérapeutique, Rev. neurol. **77**:319; 328, 1945.

12. (*a*) Davison, C.; Riley, H. A., and Brock, S.: Rhythmic Myoclonus of the Muscles of the Palate, Larynx and Other Regions, Bull. Neurol. Inst. New York **5**:94, 1936. (*b*) Faure-Beaulieu, and Gascin, R.: Etude anatomique d'un cas de myoclonies vélo-pharyngo-laryngées, Rev. neurol. **72**:734, 1939-1940. (*c*) Freeman, W.: Palatal Myoclonus: Report of Two Cases with Necropsy, Arch. Neurol. & Psychiat. **29**:742 (April) 1933. (*d*) Guillain, G.; Mollaret, P., and Bertrand, I.: Sur la lésion responsable du syndrom myoclonique du tronc cérébral, Rev. neurol. **2**:666, 1933. (*e*) Jonesco-Sisesti, N. and Hornet, T.: Le probleme du nystagmus vélo-palato-oculaire. Les dégénerescences hypertrophiques systematisées du complexe olivaire bulbaire consecutive aux lésions du noyau deutele du cervelet, Rev. d'oto.-neuro.-opht. **17**:481, 1949. (*f*) van Bogaert, L., and Bertrand, I.: Sur les myoclonies associées synchrones et rythmiques par lésions enfoyer du tronc cérébral, Rev. neurol. **1**:203, 1928.

13. This work was carried out with Dr. Edwin A. Weinstein and reported in a separate communication (Weinstein, E. A., and Bender, M. B.: Integrated Facial Patterns Elicited by Stimulation of the Brain Stem, Arch. Neurol. & Psychiat. **50**:34 [July] 1943).

was 0.8 mm., delivering minimal current, elicited first a contraction of the same side of the palate, followed by elevation of the base of the tongue and flaring of the ipsilateral nostril. With slight increases in current all these movements became more pronounced and assumed a tremulous character on continued stimulation. With stronger current the palate, the base of the tongue, and the cheek muscles showed distinct rhythmic movements. In effect, there was a palatoglossofacial myoclonus.

Further electrical explorations showed that stimulation of the central tegmental fasciculus also produced bilateral simultaneous contractions of the face, eyelids, and eyeballs. The contractions, though not rhythmic, involved many of the muscles which were implicated in our patient with myoclonus. This is significant in the light of Freeman's observations [12c] of a lesion in the central tegmental fasciculus in a patient with palatal myoclonus on the side opposite the lesion.

We did not make any studies on the effect of destruction of the inferior olivary nucleus or of other areas which correspond to lesions described in the pathologic report, namely, the dentate nucleus and the superior cerebellar peduncle. In a monkey in which we made partial lesions of the central tegmental fasciculus there was no manifest myoclonus.

The observation that palatal, facial, glossal, and probably laryngeal, myoclonus can be obtained on electrical stimulation in the region of the inferior olivary nucleus indicates that this structure has a major influence on the complex movements of muscles of the mouth, face, and eyes. This does not exclude the possibility that the dentate nucleus and other structures have a similar influence.

In correlating the clinicopathologic data and the observations made on the experimental monkey, it would appear that the inferior olivary nucleus plays an important role in the production of palatal myoclonus. Moreover, palatal myoclonus occurs when there is a change in the inferior olivary nucleus, either a destructive lesion, such as is seen in man, or an irritative focus, such as is seen in the monkey. The palatal movements produced under these conditions might be compared with ocular nystagmus, which can be produced either by destruction or by stimulation of one of the vestibular systems. For example, a lesion of the vestibular nerve or nucleus may produce vertigo, falling, and nystagmus. Similar symptoms can be induced by caloric stimulation of the normal vestibular system. It might be reasoned, then, that the influences exerted by the right and left inferior olivary nucleus on the palate or other structures of the mouth and face are in equilibrium. This is comparable to the equilibrium which is known to exist between the right and the left vestibular systems in the case of eye movements. Thus, there are equilibrium and no symptoms when the two inferior olivary nuclei are normal. If, however, one of the inferior olivary nuclei is altered, either by irritative or by destructive effects, the equilibrium is upset. The exerting influence on the palatal structures of the remaining, normal olivary nucleus results in myoclonus. Moreover, from our observations, it appears that on electrical irritation the palatal myoclonus is ipsilateral, while on destruction of the inferior olivary nucleus the myoclonus is contralateral to the lesion. It should be borne in mind that the foregoing reasonings are purely conjectural. They do not exclude theories which have been proposed to explain other types of spontaneous rhythmic movements, such as one sees in extrapyramidal disease.

SUMMARY

Eight cases of myoclonic movements of the palate and other structures are presented. Pathologic and anatomic data are described in two of these cases, in one at operation and in one at autopsy. Clinically the effect of intravenous use of drugs was observed. Electrical recordings of associated myoclonic movements in the same patient were made to determine more accurately the rate and synchrony of the movements.

It was found that intravenous injection of amobarbital (amytal®) and mephenesin (tolserol®) abolishes a type of abnormal eye movement (nystagmus on direct forward gaze) and changes the frequency and character of other abnormal eye movements. However, these drugs did not alter the myoclonic movements of the palate, larynx, pharynx, or mouth. Similarly, caloric stimulation did not affect the palatal movements, while it did produce changes in eye movements in most instances.

In Case 7 the cause was trauma, and the approximate anatomic site (verified surgically) was the left cerebellar hemisphere. The complete anatomic and pathologic picture is described and illustrated in Case 8. The sites of involvement were the left inferior olivary nucleus, right restiform body, right middle cerebellar peduncle, right dentate nucleus, and right brachium conjunctivum (superior cerebellar peduncle). The major pathologic process was demyelination.

The correlation of clinical, pathologic, and experimental data is discussed with reference to the previous reports in the literature.

CHANGES IN PHOSPHATASE ACTIVITY OF SERUM AND URINE AFTER SHOCK THERAPY

MARK D. ALTSCHULE, M.D.
AND
BARBARA H. PARKHURST, B.S.
BOSTON

THE WORK of Herlant and Timiras [1] showed that the alkaline phosphatase activity of various tissues in animals was increased after stress. In addition, Moyson [2] stated the belief that trauma caused an increase in phosphatase activity in the blood in man as a consequence of stimulation of the adrenal cortex. It was considered desirable, therefore, to study phosphatase activities in the serum of patients with mental disease before and after treatment.

MATERIAL AND METHODS

Thirty-nine patients, ranging in age from 14 to 79 years, were studied; 13 were men. The diagnoses were distributed as follows: schizophrenia, 13 patients; manic-depressive psychosis (manic phase), 4; manic-depressive psychosis (depressed phase), 9; involutional psychosis, 6, and severe neurosis, 7. No patients with skeletal injuries were included.

Blood was taken in all instances before any treatment was given; in addition, blood was taken in 27 instances approximately one week after the last ambulatory insulin or electroshock treatment. In three instances blood was taken immediately before, and again four hours after, the first electroshock treatment given to these three patients. The method of Seligman and associates,[3] was used for estimating the phosphatase activity of serum. Dr. H. A. Ravin, working in Dr. Seligman's laboratory, made estimations on eight samples of blood; the values obtained by him agreed with those obtained in this laboratory.

Acid phosphatase activity of samples of urine, obtained on the same days as the blood samples, was measured by means of a method described elsewhere [4]; the values shown here are the averages for determinations made on two specimens of urine voided 90 minutes apart in the early morning.

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School.

1. Herlant, M., and Timiras, P. S.: Alkaline Phosphatases in Various Tissues of the Rat During the Alarm-Reaction, Endocrinology **46**:243, 1950.

2. Moyson, F.: Recherches sur l'hyperphosphatasémie post-traumatique, Acta clin. belg. **5**:297, 1950.

3. Seligman, A. M.; Chauncey, H. H.; Nachlas, M. M.; Manheimer, L. H., and Ravin, H. A.: Colorimetric Determination of Phosphatases in Human Serum, J. Biol. Chem. **190**:7, 1951.

4. Altschule, M. D.; Parkhurst, B. H., and Zager, G. R.: Measurement of Urinary Acid Phosphatase Activity, Am. J. Clin. Path. **21**:480, 1951.

OBSERVATIONS

The alkaline phosphatase activity of the serum of untreated patients was between 0.70 and 4.20 units per 100 ml. (Chart 1); the level of activity did not vary with the different diagnostic categories studied. The distribution of values was similar to that reported in normal subjects by Seligman and associates.[3] The values were the same when measured four hours after an electroshock treatment (Table 1). On 22 patients studies were made after a course of 5 to 20 electroshock treatments or after 30 to 110 ambulatory insulin treatments. Sixteen of these patients showed improvement; 6 showed no change, and 10 exhibited a decrease in the level of alkaline phosphatase activity in the serum (Chart 2). Of six patients not improved after treatment, two showed no change in activity, three an increase, and one a decrease.

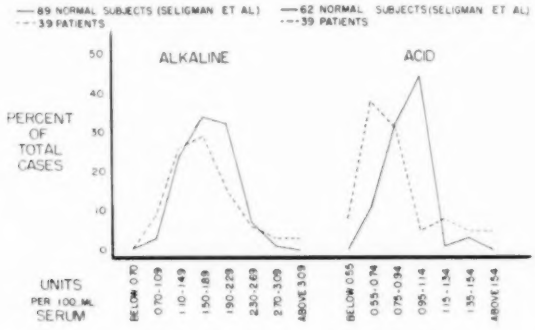

Chart 1.—Phosphatase activities of serum in untreated patients.

TABLE 1.—*Serum Phosphatase Activity* Before and Four Hours After First Electroshock*

Patient	Alkaline Phosphatase		Acid Phosphatase	
	Before	After	Before	After
Be	1.46	1.26	0.73	0.95
Ma	2.30	2.40	0.78	0.80
P	1.20	1.30	0.75	0.85

* Expressed in units per 100 ml. of serum.

The acid phosphatase activity of the serum of untreated patients ranged from 0.43 to 1.86 units per 100 ml.; the degree of activity in all patients was in the same range, irrespective of the diagnostic category. The distribution of values (Chart 1) showed a preponderance of low ones. Of 27 patients, studies made after treatment showed increases in 2, no change in 12, and decreases in 13; the 2 patients in whom increases occurred, as well as most of those who showed no significant change, had low initial values. Correlation of the direction of change and the occurrence of improvement was not evident (Chart 3).

Urinary acid phosphatase activity was unchanged after treatment in one patient (Mc) whose condition was not improved (Table 2); it was lower in the other six who were discharged as improved, but the amount of change found may not be significant in all cases, in view of the pronounced variations that may occur spontaneously.

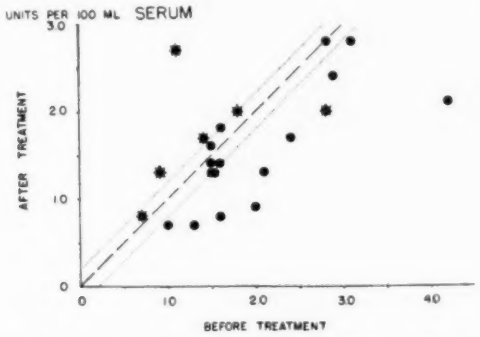

Chart 2.—Changes in alkaline phosphatase activity of serum after treatment. Dots show values for patients who were improved; stars show values for patients who were not improved. Points to the right of the broken line represent decreases after treatment; the dotted lines enclose the range of spontaneous variation.

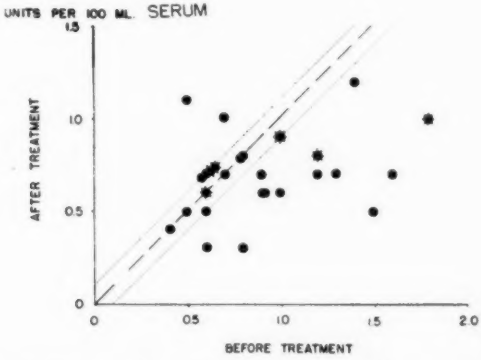

Chart 3.—Changes in acid phosphatase activity after treatment. Dots show values for patients who were improved; stars show values for patients who were not improved. Points to the right of the broken line represent decreases after treatment; the dotted lines enclose the range of spontaneous variation.

COMMENT

Gottfried and Willner [5] found alkaline phosphatase activity of serum to be normal in patients with schizophrenia. The results of the present study show that alkaline and acid phosphatase activities of serum and the acid phosphatase activity of urine

5. Gottfried, S. P., and Willner, H. H.: Blood Chemistry of Schizophrenic Patients Before, During and After Insulin Shock Therapy: Preliminary Studies, Arch. Neurol. & Psychiat. **62**:809 (Dec.) 1949.

in untreated patients with schizophrenic, manic-depressive, and involutional psychoses or with severe neuroses, are all in the normal range; serum acid phosphatase activity usually is low in this range. The occurrence in several instances of values for alkaline phosphatase that were higher than any found by Seligman and associates [5] is due to the inclusion of several patients between 14 and 17 years of age; young subjects commonly exhibit much higher levels of serum alkaline phosphatase activity than those found in older subjects.[6]

Moyson's [2] finding of increases in blood alkaline phosphatase activity for a period of one or two hours after trauma led him to conclude that these changes were indicative of increased activity of the adrenal cortex; the validity of this conclusion is weakened by the brief duration of the changes in activity. In addition, increases in phosphatase activity were not found by others in studies carried out over longer periods after trauma.[7] Furthermore, single electroshock treatments, which are known to cause marked activation of the adrenal cortex, had no effect on serum phosphatase activities. Although experiments in animals have shown

TABLE 2.—*Effects of a Course of Treatment on Urinary Acid Phosphatase* Activity*

Patient	Sex	Age	Before Treatment	After Treatment
I	M	26	300 ± 14	161 ± 15
G	M	21	259 ± 26	237 ± 3
Ba	M	64	123 ± 3.5	8 ± 4
Bu	F	28	67 ± 9	14 ± 5
W	F	34	10 ± 1	4 ± 1
Bo	F	32	13 ± 2	1 ± 0.5
Mc	F	27	13 ± 2	18 ± 14

* Expressed in units per 100 ml. of urine.

that stress increases the alkaline phosphatase activity of the organs studied,[1] it cannot be assumed that the blood must necessarily exhibit the same changes.

Consideration of the effects on tissue phosphatase activities of adrenalectomy in animals,[8] of the injection of corticotropin,[9] or of the administration of adreno-

6. Clark, L. C., and Beck, E. I.: Plasma "Alkaline" Phosphatase Activity: I. Normative Data for Growing Children, J. Pediat. **36**:335, 1950.

7. Fairlie, C. W.; Barss, T. P.; French, A. B.; Jones, C. M., and Beecher, H. K.: Metabolic Effects of Anesthesia in Man: IV. A Comparison of the Effects of Certain Anesthetic Agents on the Normal Liver, New England J. Med. **244**:615, 1951.

8. Kochakian, C. D., and Vail, V. N.: Effect of Adrenalectomy, Adrenal Cortex Extract, and Adrenal Cortex Extract, Plus Testosterone Propionate on the Phosphatases of Rat Tissues, J. Biol. Chem. **156**:779, 1944. Folley, S. J., and Greenbaum, A. L.: Effects of Adrenalectomy and of Treatment with Adrenal Cortex Hormones on the Arginase and Phosphatase Levels of Lactating Rats, Biochem. J. **40**:46, 1946. Vail, V. N., and Kochakian, C. D.: Effect of Adrenalectomy, Adrenal Cortical Hormones, and Testosterone Propionate Plus Adrenal Cortical Extract on the "Alkaline" and "Acid" Phosphatase of the Liver and Kidney of the Rat, Am. J. Physiol. **150**:580, 1947.

9. Li, C. H.; Kalman, C.; Evans, H. M., and Simpson, M. E.: Effect of Hypophysectomy and Adrenocorticotropic Hormone on the Alkaline Phosphatase of Rat Plasma, J. Biol. Chem. **163**:715, 1946. Li, C. H.; Kalman, C., and Evans, H. M.: Effect of Hypophyseal Growth Hormone on the Alkaline Phosphatase of Rat Plasma, ibid. **169**:625, 1947.

cortical hormones [10] is not helpful, as the reported findings are highly discordant. Similar confusion exists concerning the effects of hypophysectomy [11]; there is additional difficulty in this respect, owing to the fact that hypophysectomy has effects other than depression of adrenocortical function. In a study in man reported in 1940, Watson [12] described a large decrease in serum alkaline phosphatase activity following injection of an adrenal cortex preparation; his initial values, however, were greatly elevated above the normal range. It is evident that no final conclusion can be drawn concerning the importance of adrenocortical function in the regulation of phosphatase activity.

After a course of ambulatory insulin treatments or of electroshock therapy, the serum alkaline phosphatase level was significantly lower in most of the patients who showed improvement and was unchanged or higher in those who did not; similar changes occurred in the urinary acid phosphatase activity. Most patients also showed either a decrease or no change in acid phosphatase activity of the serum after treatment; it is possible that failure of the serum acid phosphatase activity to fall more regularly with improvement was due to the low values occurring before treatment.

The present state of knowledge concerning these enzymes does not permit interpretation of the results of the present study. For the present, the decrease in phosphatase activities found to occur commonly after treatment should be regarded only as further evidence of lasting biochemical change caused by shock therapies; interpretation of these findings in relation to possible changes in pituitary-adrenocortical function cannot be made with assurance.

SUMMARY AND CONCLUSIONS

Alkaline and acid phosphatase activities of serum and acid phosphatase activity of urine all are in the normal range in patients with schizophrenic, manic-depressive, or involutional psychoses, or with severe neuroses; serum acid phosphatase activity appears to be low in the normal range.

Single electroshock treatments do not affect serum alkaline or acid phosphatase activities. A course of electroshock or ambulatory insulin treatments commonly results in lowering of phosphatase activities.

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10. Footnote 8. Williams, H. L., and Watson, E. M.: Influence of Hormones upon the Phosphatase Content of Rat Femurs: I. Effects of Adrenal Cortical Substances and Parathyroid Extract, Endocrinology **29**:250, 1941. Kochakian, C. D., and Bartlett, M. N.: Effect of Crystalline Adrenal Cortical Steroids, DL-Thyroxine, and Epinephrine on the Alkaline and Acid Phosphatases and Arginase of the Liver and Kidney of the Normal Adult Rat, J. Biol. Chem. **176**:243, 1948.

11. Li and associates.[9] Jones, L. M., and Shinowara, G. Y.: Serum Inorganic Phosphate and "Alkaline" Phosphatase Activity in Hypophysectomized Rats, J. Biol. Chem. **142**:935, 1942. Buchwald, K. W., and Hudson, L.: Biochemical Effects of Injections of Sex Hormones into Hypophysectomized Rats, Endocrinology **41**:111, 1947. Verne, J., and Hébert, S.: Étude histochimique des phosphatases alcalines de l'intestin du rat dans leurs rapports avec la corticosurrénale, Compt. rend. Soc. biol. **142**:300, 1948. Mathies, J. C., and Gaebler, O. H.: Effect of Growth Hormone Preparations on Alkaline Phosphatase of the Tibia, Endocrinology **45**:129, 1949. Mathies, J. C.; Gaebler, O. H., and Palm, L.: Effect of Growth Hormone on Hepatic and Renal Acid and Alkaline Phophatases, ibid. **45**:480, 1949.

12. Watson, E. M.: Effect of Adrenal Cortical Extract on the Serum Phosphatase in Chronic Arthritis, Endocrinology **27**:521, 1940.

BLOOD GLUTATHIONE LEVEL IN MENTAL DISEASE BEFORE AND AFTER TREATMENT

MARK D. ALTSCHULE, M.D.
ELAINE P. SIEGEL
AND
DOROTHY H. HENNEMAN, M.D.
BOSTON

OBSERVATIONS on the level of glutathione in the blood in patients with mental disease have been recorded by a number of authors during the past three decades.[1] Recent work on the relation between glutathione concentration and activity of the adrenal cortex [2] made it desirable to study further the changes in the blood glutathione level that occur in patients with mental disorders, particularly those receiving shock treatment.

MATERIAL AND METHODS

One hundred and twenty-one patients, ranging in age from 18 to 82, were studied; 47 were men. The diagnoses varied (Chart 1). The blood glutathione content was measured as described previously [3]; the results are expressed in terms of milligrams of glutathione per 100 ml. of erythrocytes, since all the polypeptide in the blood is in the red cells. Patients with blood

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass., and the Department of Medicine, Harvard Medical School.

1. (*a*) King, E. J.; Baumgartner, L., and Page, I. H.: Glutathiongehalt des Blutes von Geisteskranken, Biochem. Ztschr. **217**:389, 1930. (*b*) Gullota, S.: Il glutatione nel sangue di alcuni malati di mente e dei dementi precoci in ispecie, Boll. Soc. ital. biol. sper. **6**:499, 1931. (*c*) Looney, J. M., and Childs, H. M.: Lactic Acid and Glutathione Content of Blood of Schizophrenic Patients, J. Biol. Chem. **105**:liii, 1934; (*d*) Lactic Acid and Glutathione Content of Blood of Schizophrenic Patients, J. Clin. Invest. **13**:963, 1934. (*e*) Brice, A. T., Jr.: The Blood Glutathione (GSH) Level in Mental Diseases, Am. J. Psychiat. **91**:1389, 1935; (*f*) Fat Feeding in Schizophrenia, J. Nerv. & Ment. Dis. **84**:152, 1936. (*g*) Ljungberg, E.: The Glutathione Content of the Blood in Schizophrenia, Acta psychiat. et neurol. **11**:369, 1937. (*h*) Gerundo, M., and Corwin, W. W.: Blood Lipoids in Dementia Praecox and During Insulin Shock Therapy, J. Nerv. & Ment. Dis. **90**:464, 1939. (*i*) Ljungberg, E.: Some Observations on Behavior of Blood Glutathione Particularly During Insulin Shock Therapy, Acta psychiat. et neurol., Supp. 47, p. 172, 1947. (*j*) Henneman, D. H., and Altschule, M. D.: Immediate Effects of Shock Therapies, Epinephrine and ACTH on Blood Glutathione Level of Psychotic Patients, J. Appl. Physiol. **3**:411, 1951. (*k*) Caren, R., and Carne, H. O.: The Blood Glutathione Level and Its Response to Insulin in Diabetic and Non-Diabetic Patients and a Case of Insulin Resistance, Am. J. M. Sc. **221**:307, 1951.

2. (*a*) Conn, J. W.; Louis, L. H., and Johnston, M. W.: Alleviation of Experimental Diabetes in Man by Administration of Reduced Glutathione (GSH): Metabolic Implications, Science **109**:279, 1949. (*b*) Seneca, H.; Ellenbogen, E.; Henderson, E.; Collins, A., and Rockenbach, J.: The in Vitro Production of Cortisone by Mammalian Cells, ibid. **112**:524, 1950.

hematocrit values below 38% were excluded from this study because of the increase in erythrocytic glutathione content that occurs in anemia.[3] Duplicate measurements were made on patients shortly after admission and again not less than five days after the last of a course of electroshock or ambulatory insulin treatments.

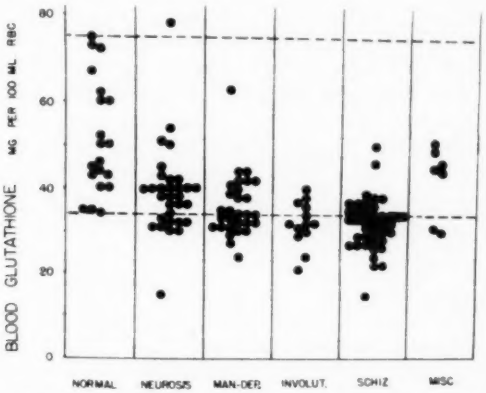

Chart 1.—Blood glutathione level in normal subjects and in untreated patients.

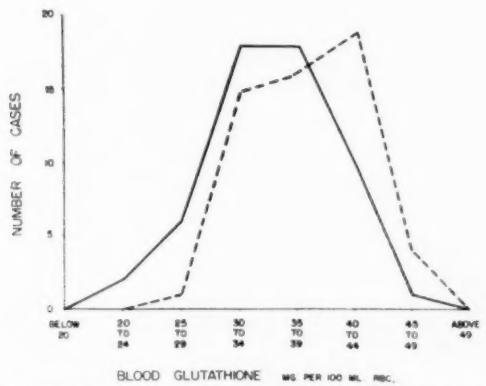

Chart 2.—Blood glutathione level in 55 patients before (solid line) and after (line of dashes) a course of shock treatments.

OBSERVATIONS

Initial Levels.—Patients with schizophrenia, manic-depressive psychoses, or involutional psychosis had levels of blood glutathione in or below the lower normal range (Chart 1). A similar finding was observed in some, but not all, of the neurotic patients. Two patients with psychoses associated with drug intoxication and three patients with senile psychoses had normal values. One with a psychosis associated

3. Dogliotti, G. C., and Castellani, T.: Glutatione e anemie, Boll. Soc. ital. biol. sper. **10**:521, 1935.

with mental deficiency and one with an unclassified psychosis had low values (Chart 1). In spite of the diversity of diagnoses, the distribution of values for patients with severe neuroses and with schizophrenic, manic-depressive, and involutional psychoses was that of a homogeneous group (Chart 2).

Spontaneous Variations.—Measurements were made from one to six days apart before treatment in 15 instances; the differences between the two readings ranged from 0 to ± 5.5 mg. per 100 ml. of erythrocytes, with an average of ± 2.23 mg. For four untreated patients measurements were made from 21 to 52 days apart; the differences between the two values ranged from ± 2.5 to ± 3.5 mg. per 100 ml. of erythrocytes, with an average of ± 2.88 mg. The average deviation for the entire group of 19 patients was ± 2.37 mg. per 100 ml. of erythrocytes for measurements

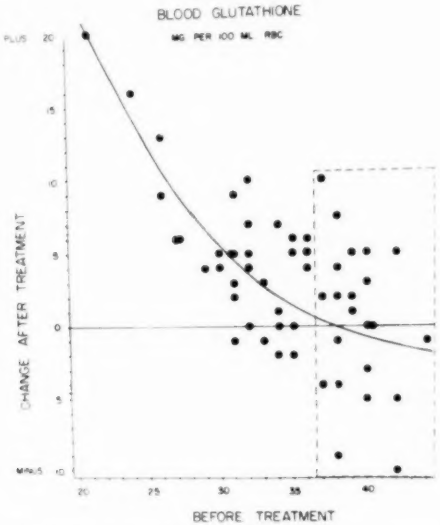

Chart 3.—Amount of change in blood glutathione level after a course of shock treatments. The area enclosed by the dotted lines shows that no consistent change occurs in patients in whom the initial level is normal.

made from 1 to 52 days apart on untreated patients whose clinical status did not change in the interval.

Effects of Shock Treatments.—After the end of the period of treatment, patients with values of 36 mg. per 100 ml. of erythrocytes or below showed increases varying in amount inversely to the initial levels (Chart 2). Thirty-three patients had initial values in the range of 22 to 36 mg. per 100 ml. Of these, 3 patients showed no change; 4 showed decreases of 1 or 2 mg., and 25 showed increases ranging as high as 20 mg. per 100 ml. of erythrocytes. The average change for the entire group was + 5.0 mg. Twenty-two patients had initial blood glutathione levels of from 37 to 44 mg.; in this group, 2 showed no change after treatment, 11 showed increases averaging 4.06 mg., and 9 showed decreases averaging 4.66 mg. The average change for the entire group was + 0.18 mg. (Chart 3).

COMMENT

In corroboration of the findings of earlier workers, the glutathione content of blood, expressed as milligrams per 100 ml. of erythrocytes, was found to be low in patients with schizophrenic, manic-depressive, and involutional psychoses; in addition, low values were found for some patients with severe neuroses. Spontaneous variations in the blood glutathione level occur and introduce uncertainties in the interpretation of results of studies. The causes of these variations are not known, but one factor may be marked stasis in the extremities, such as occurs in many patients with mental diseases [4]; blood that has been made hypoxic yields higher values for glutathione than the same blood does at higher oxygen tensions.

After treatment, the blood glutathione level rose in those patients whose initial levels were low and did not rise in those for whom normal values were found before treatment; the degree of rise varied with the difference between the patient's control level and the normal range.

Earlier work showed that the glutathione concentration of blood rises during insulin [1i,j] or electroshock [1j] treatment; these increases are transitory, lasting only a few hours, after which a fall to, or toward, the initial values occurs. After a course of treatments the level, if low before treatment, becomes normal. A rise to normal of

Changes in Blood Glutathione Level During Relapse*

	Case W	Case D
Before treatment	26-28	33
At end of treatment	31	35-37
In relapse	20-28	30-32

* Expressed in milligrams per 100 ml. of erythrocytes.

an initially low glutathione level is no indication of the degree of permanence of the clinical improvement that occurred. When clinical relapse occurs, the blood glutathione level falls (Table). The small changes that may occur after treatment and the occurrence of spontaneous variations unrelated to treatment make it impossible to use single measurements of the blood glutathione level as an index of the severity of the disease or the degree of improvement.

The significance of the observations made here cannot be stated with certainty because of several facts. Methods used for measuring glutathione are not specific for that substance. In addition, the role of glutathione in metabolic processes is not completely understood. Nevertheless, the finding of Conn and associates [2a] that glutathione counteracts the activity of corticotropin and the finding of Seneca and associates [2b] that this inhibition is due to prevention of synthesis of cortisone-like substances by the adrenal cortex may be pertinent. If the low blood glutathione level found in patients with various mental diseases is indicative of similar lowering of its concentration in the adrenal cortex, it might be concluded that a given degree of stimulation of the anterior lobe of the pituitary gland under conditions of stress would result in the production of an abnormally large amount of cortisone-like hormones in such a patient. The effect of these hormones in causing psychoses in some normal persons and in producing exacerbations in some with psychoses is well

4. Altschule, M. D., and Sulzbach, W. M.: Effect of Carbon Dioxide on Acrocyanosis in Schizophrenia, Arch. Neurol. & Psychiat. **61**:44 (Jan.) 1949.

known. However, attempts to relate the low blood glutathione level found in patients with mental disease to the mechanisms producing these disorders is entirely speculative. Attempts to obtain data concerning this matter by giving 4 or 5 gm. of glutathione intravenously were unsuccessful because of the severe chills, followed by high fever, that occurred early in the course of the infusion.

The role of glutathione in intermediary carbohydrate metabolism is well known; it acts in concert with the enzyme glyoxalase.[5] Although glyoxalase activity of the blood is normal in manic-depressive and schizophrenic patients,[6] the possibility must be considered that the lowered blood glutathione seen in these and other mental disorders may be responsible for the impairment of carbohydrate metabolism seen in these diseases. This problem is being studied in this laboratory.

SUMMARY AND CONCLUSIONS

The blood glutathione level is in or below the lower normal range in untreated patients with manic-depressive, involutional, or schizophrenic psychoses; some patients with severe neuroses show the same change.

After courses of electroshock or ambulatory insulin treatments that result in improvement, the blood glutathione level rises to, or toward, the normal if initially low; little or no change occurs if the initial concentration of blood glutathione is not low.

The significance of the findings is discussed.

5. Racker, E.: The Mechanism of Action of Glyoxalase, J. Biol. Chem. **190**:685, 1951.

6. Franks, W. R., and Proctor, L. D.: The Blood Glyoxalase Activity of a Series of Mentally Normal and Mentally Ill Persons, Am. J. Psychiat. **97**:1403, 1941.

DOES NYSTAGMUS OCCUR IN LESIONS OF THE CERVICAL CORD?

CARL B. BOOTH, M.D.
CHESTNUT HILL, MASS.

RECENT reports [1] have called attention to the importance of a differential diagnosis of supracervical and cervical lesions, especially those due to herniated cervical disk. Some authors have observed that nystagmus is associated with lesions of the cervical portions of the cord. Obviously, it is then important, for diagnostic purposes, to determine the frequency of nystagmus in cervical lesions. In view of the relative paucity of reports in the literature, it was decided to investigate this matter.

REVIEW OF THE LITERATURE

Kraus and Silverman [2] reported one case of osteofibroma of the odontoid process with nystagmus, one of intramedullary glioma at the third cervical segment with nystagmoid jerks, and one of intramedullary sarcoma at the first to the fourth cervical segment with distinct nystagmus to the right.

Nystagmus has even been discovered in association with lesions of the thoracic segments. Thus, Wiersma [3] reported an intradural fibroma at the seventh to the eighth thoracic segment with distinct horizontal nystagmus, which disappeared after operation.

Hawk [5] reported a case of herniated intervertebral disk in the region of the fourth cervical vertebra with fine lateral nystagmus in either direction. Smith and Riesenman [6] cited a case of compression fracture of the body of the third cervical vertebra accompanied with nystagmus, the latter disappearing after reduction of the fracture. They ascribed the nystagmus to compression of the spinocerebellar

From the Division of Neuropsychiatry, Montefiore Hospital for Chronic Diseases, New York.

Postdoctorate Research Fellow, National Institute of Mental Health, United States Public Health Service.

1. Strully, K. J.; Gross, S. W.; Schwartzman, J., and von Storch, T. J. C.: Progressive Spinal Cord Disease, J. A. M. A. **146**:10 (May 5) 1951. Bucy, P. C.; Heimburger, R. F., and Oberhill, H. R.: Compression of the Cervical Spinal Cord by Herniated Intervertebral Discs, J. Neurosurg. **5**:471 (Sept.) 1948. Bucy, P. C.: Simulation of Multiple Sclerosis and Other Degenerative Diseases of the Spinal Cord by Herniation of Cervical Intervertebral Discs, Mississippi Valley M. J. **71**:85 (May) 1949.

2. Kraus, J. W., and Silverman, N. E.: Facial Paresis as a Manifestation of Tumors of the Upper Half of the Cervical Spinal Cord, J. Neurol. & Psychopath. **7**:132 (Oct.) 1926.

3. Wiersma, D.: Clinical and Anatomical Experiences in 2 Cases of Spinal Cord Tumour, Acta psychiat. et neurol. **3**:63, 1928.

4. Footnote deleted by the author.

5. Hawk, W. A.: Spinal Compression Caused by Ecchondrosis of the Intervertebral Fibrocartilage, with a Review of the Recent Literature, Brain **59**:204, 1936.

6. Smith, H. C., and Riesenman, F. R.: Unusual Forms of Nystagmus, Arch. Ophth. **33**:13 (Jan.) 1945.

pathways. Abrahamson and Grossman [7] reported two cases of compressive lesions at the level of the foramen magnum with nystagmus. Elsberg [8] mentioned the case of an intradural sarcoma extending from the fourth cervical segment and projecting into the foramen magnum, with compression of the neuraxis and resultant nystagmus, which disappeared after removal of the mass. Elsberg and Strauss [9] later reported a case of an endothelioma of the cord, of which about one-third projected upward through the foramen magnum. Symonds and Meadows [10] presented three cases of lesions compressing the upper cervical portion of the cord (with nystagmus), all of which, however, extended through the foramen magnum. Haynes [11] reported an interesting case of a herniated intervertebral disk between the fifth and the sixth cervical vertebra, lying on the right side of the cord and compressing it. There was a constricting ring of dura just below the foramen magnum, causing a complete block. He observed a fine, sustained nystagmus when the patient looked to the left.

Walsh [12] stated: "In syringomyelia and syringobulbia nystagmus of the rotatory type is commonly seen. Its etiology is not known. Probably it is due to involvement either of the vestibular nuclei or of the vestibular tracts."

In his textbook, Brain [13] stated: "Nystagmus is sometimes seen after a lesion of the cervical region of the spinal cord, and is then probably due to defect of afferent impulses from the cervical spine."

From the foregoing case reports it is apparent that, in the majority of instances, the nystagmus was associated with lesions of the upper cervical segments (four cases) or in the region of the foramen magnum (nine cases).

MATERIAL AND FINDINGS

The charts of 115 patients hospitalized at the Montefiore Hospital for Chronic Diseases with lesions of the spinal cord were reviewed. Of these patients, 46 presented lesions in the cervical region. In 4 of the 46 cases, nystagmus was said to have been present. Cases in which only nystagmoid jerks were described were discarded.

In two of these cases the diagnosis was confirmed at autopsy. In the first case the lesions consisted of an angioma of the cord with secondary syringomyelia extending from the second to the sixth cervical segment. The brain was not available for study. Nystagmus was recorded in this case, but the type was not described. The second case was that of a metastatic lymphosarcoma compressing

7. Abrahamson, I., and Grossman, M.: Tumors of the Upper Cervical Cord, Tr. Am. Neurol. A. **47**:149, 1921.

8. Elsberg, C. A.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, Inc., 1925, p. 50.

9. Elsberg, C. A., and Strauss, I.: Tumors of the Spinal Cord Which Project into the Posterior Cranial Fossa, Arch. Neurol. & Psychiat. **21**:261 (Feb.) 1929.

10. Symonds, C. P., and Meadows, S. P.: Compression of the Spinal Cord in the Neighborhood of the Foramen Magnum, Brain **60**:52 (March) 1937.

11. Haynes, W. G.: Dural Constricting Ring with Cervical Protruded Intervertebral Disc: Report of a Case, New England J. Med. **227**:825 (Nov. 26) 1942.

12. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, p. 1238.

13. Brain, W. R.: Diseases of the Nervous System, New York, Oxford University Press, 1947, p. 76.

the upper cervical segments. Again, the brain was not available for study. Nystagmus was noted in all directions. In this case, however, there were signs pointing to involvement of other cranial nerves or the brain stem, namely, weakness of the left superior rectus; convergence weakness, more pronounced on the right; weakness of the left lower facial muscles, and fibrillary tremors of the tongue. In the third case the diagnosis at operation was considered to be "intramedullary disease" involving the third and fourth cervical segments of the cord. A coarse, slow nystagmus on right lateral gaze was noted. In the fourth case the clinical diagnosis was syringomyelia with evidence of involvement from the second cervical through the third thoracic segment. There was slight rotatory nystagmus on looking to the left.

Thus, in 4 of 46 cases nystagmus has been recorded in association with lesions involving the upper cervical segments of the cord. It must be noted, however, that, with the information at hand, a possible lesion above the foramen magnum could not be excluded. It is realized, furthermore, that in a study of this nature it is difficult to ascertain the accuracy with which nystagmus was observed.

COMMENT AND CONCLUSIONS

From this investigation one can merely speculate regarding the possible mechanisms whereby nystagmus may be produced by lesions of the cervical portion of the cord. Since the medial longitudinal fasciculus extends to the upper cervical segments,[14] it is conceivable that interruption of this pathway might produce nystagmus. This is unlikely, however, for Strong and Elwyn [14] stated that below the vestibular nuclei the fibers of this tract are all descending. Involvement of the spinocerebellar tracts might conceivably cause nystagmus. Another possible mechanism is the effect of traction on the medulla with secondary involvement of vestibular pathways. Such an explanation would be applicable particularly to extramedullary lesions of the cord.

These attempts at explanation are, of course, only hypotheses, none of which has been proved. This study serves principally to indicate that nystagmus is an uncommon occurrence in association with lesions of the cervical region of the spinal cord. In the differential diagnosis of cervical and supracervical lesions, therefore, the presence of nystagmus strongly indicates a supracervical disorder.

14. Strong, O. S., and Elwyn, A.: Human Neuroanatomy, Ed. 2, Baltimore, Williams & Wilkins Company, 1948, p. 230.

NONAPHASIC MISNAMING (PARAPHASIA) IN ORGANIC BRAIN DISEASE

EDWIN A. WEINSTEIN, M.D.
AND
ROBERT L. KAHN, M.A.
NEW YORK

IN A GROUP of patients with altered behavior in association with intracranial disease [1] a type of language disorder was noted in which an incorrect term was substituted for the proper name of an object. Such misnaming has been generally classed as "verbal paraphasia." It has been considered a type of receptive aphasia [2] and has been attributed to a lesion in the Wernicke area. In the present study of 30 patients an attempt has been made to investigate the relation of this alteration in language to (1) aphasia, (2) the character and localization of the anatomical lesion, (3) the concomitant abnormalities in the electroencephalogram, and (4) the associated alterations of behavior.

MATERIAL AND METHOD

Of the 30 patients, 19 had brain tumors; 7 had subarachnoid hemorrhage from aneurysms of the circle of Willis; 1 had a head injury; 2 had meningoencephalitis, and in 1 the disturbance in language appeared during intensive electric convulsion therapy for intractable pain from a neoplasm of the spinal cord. Of the 19 neoplasms, 5 were of metastatic origin; 4 were in the region of the third ventricle; 4 were bifrontal; 4 infiltrated the right (nondominant) temporal lobe, and 2 were acoustic neurinomas. Except for three of the third-ventricle tumors and one bifrontal tumor which compressed the third ventricle, all were associated with increased intracranial pressure. Electroencephalographic records were obtained on 26 patients.

The data were collected partly by formal tests in which specific objects were shown to the patient, who was then asked to name them. The list of objects was predetermined to include a number of items that were found primarily in a hospital or were associated with illness, such as a syringe, tongue blade, thermometer, wheel chair, and adhesive tape. For some of these objects it was not expected that the patient would give the precise technical or categorical name, and a correct functional description was acceptable. Other objects shown were of the type familiar in everyday life and had no particular connection with illness. These tests were repeated frequently. In addition, each patient was subject to almost daily interviewing, so that our observations include spontaneous speech and answers to questions that were not specifically designed to test naming ability.

This study was aided by the Neurological Research Fund.

From the Neurological Service of the Mount Sinai Hospital.

Read at the Seventy-Sixth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 20, 1951.

1. Weinstein, E. A., and Kahn, R. L.: (*a*) The Syndrome of Anosognosia, Arch. Neurol. & Psychiat. **64**:772-791 (Dec.) 1950; (*b*) Patterns of Disorientation in Organic Brain Disease, J. Neuropath. & Clin. Neurol. **1**:214-226, 1951.

2. Weisenburg, T., and McBride, K. E.: Aphasia: A Clinical and Psychological Study, New York, Commonwealth Fund, 1935.

OBSERVATIONS

The substituted name, in almost all instances, was related to the object in terms of certain aspects of its function or structure. A radiator was called a "stove," while a slipper was called a "wallet" because, the patient explained, "they put money in it." In other cases the name given bore no logical functional relationship to the object but appeared to be related to some structural or perceptual aspect. Thus, a tongue blade was called a "ruler"; a hypodermic needle, a "cigarette holder"; a wheel chair, a "spinning wheel," and a pocket flashlight, an "imitation cigar." Usually the substituted name represented a combination of responses to structural and functional components. For example, a wallet was called a "bankbook"; a medicine cabinet, a "bookcase"; a penknife, a "nail file," and a bedpan, a "saucer."

The following case is illustrative.

E. K., a woman aged 52, was admitted to the hospital on Aug. 1, 1950, with a history of blackouts for three years and grand mal seizures for two years. A change of personality had been noted for three years; she had become lazier, more dependent and demanding, and was banal, gossipy, and repetitive. Neurological examination showed only bilateral anosmia. X-ray examination of the skull showed calcification just to the right of the midline. The electroencephalogram revealed a delta focus at the right frontal electrodes. Lumbar puncture yielded a clear fluid under normal pressure, containing 192 mg. of protein per 100 cc. A pneumoencephalogram showed a filling defect of the left ventricle and a pushing upward of the right lateral ventricle by the dilated third ventricle. On Aug. 11 an olive-sized meningioma, extending bilaterally back to the optic chiasm, was removed from the floor of the anterior fossa by Dr. Benno Schlesinger. After operation the patient was stuporous, and it was not until Aug. 23 that she responded to questions.

At that time, and for the next two months, the patient manifested anosognosia, disorientation, and misnaming; was incontinent of urine, and on double simultaneous cutaneous stimulation showed extinction and displacement. Her electroencephalogram was reported by Dr. H. Strauss as showing bilateral diffuse delta activity having a frequency of 3 to 6 cps, with frequencies of 2 cps in the frontal areas. At first the patient denied having had an operation. She claimed that the scars on her head were due to a fall that she had had a year before and explained her lack of hair by stating that she had got a haircut to keep cool. When she was asked why she was in the hospital, her usual response was that she had "hysteria." On September 14, for the first time, she admitted having had an operation but minimized its importance, saying, "They might as well have operated on my hand or arm and got the same result." She would talk about the operation as though she was not really convinced: "Well, they tell me I had an operation."

She was disoriented for time of day, with confusion of morning and afternoon, and gave the year repeatedly as 1940. In her disorientation for place she showed verbal identification, stating that she was both home and in a hospital, and she displaced the location of the hospital to Queens (where she lived). For several weeks the patient was affable and euphoric, but soon after admitting her operation she became restless and paranoid, accusing the staff of having operated on her without her knowledge. The paranoid episode lasted two weeks.

On double simultaneous tactile stimulation to her cheek and extremities, the patient showed extinction and displacement of one stimulus. Thus, if she was touched on the face and hand, she would feel only the stimulus to the face. If her hand was resting on her thigh, she would point to her face and the thigh underlying the hand that had been touched. This would occur even when the patient kept her eyes open and observed where she was being touched. At times the patient displaced stimuli into space or on to the examiner. This perceptual disturbance persisted during her hospitalization, although in the later stages there was displacement only with her eyes closed.

The patient misnamed only objects related to the hospital environment. A syringe was called "part of a percolator." At different times a wheel chair was called a "chaise longue," a "Morris chair," and an "easy chair." A tongue blade was called an "emery board" and a "shoe horn." A pocket flashlight was called "some kind of pen or pencil." On one occasion, when the examiners were trying to convince her that she was not home but in a hospital, she was asked about the adjoining bed. She insisted that it was a "studio couch" and that visitors frequently used it. After her discharge, the patient was again examined, on Feb. 19, 1951. At that time she showed no disorientation and was completely aware of her operation and preceding illness. She called a syringe a "thermometer" but misnamed no other objects. Errors on double simultaneous cutaneous stimulation occurred only with her eyes closed and her arms crossed. She was amnesic for most of the events of her hospital stay.

As in the case just described, misnaming was most frequently obtained with objects that bore a relation to the patient's personal problems, mainly those of his illness. Thus, a hospital object like the glass drinking-tube was variously named a "cigarette," "stirrer," "quill," and "pipe for smoking." Doctors were typically misnamed, being referred to by such terms as "lawyer," "white-collar workers," "chief of crew," "one of the presidents," "bartender," "supervisor of insurance," and "credit manager." One of us (E. A. W.) was named by such variations as "Weinberg," "Weingarten," "Weiner," and "Wiseman," a type of misnaming that did not occur in patients without paraphasia. An unmarried woman with a frontal-lobe tumor who denied her illness, saying that she had come to the hospital to find a husband, referred to the other patients in the ward as "potential mothers." When patients were asked in what kind of place they were, they substituted euphemisms for the hospital, such as "sanatorium," "a dump for rest and relaxation," and a "menagerie." A patient with problems of sexual inadequacy referred to his penis as a "cigarro."

In no case did the misnaming appear as an isolated manifestation, but in all instances was associated with other disturbances in behavior. All 30 patients had disorientation for place and time. Delusions, mainly denial of illness or defect (anosognosia), were present in 27 patients. Confabulations were noted in 24 patients, and incontinence of urine, in 21. Paranoid or euphoric behavior was noted in 21 patients, and misnaming was sometimes incorporated in their humor. Thus, one woman called the curtain rod by her bed a "trapeze," and another referred to the bedpan as a "piano stool."

In 25 of 26 patients bilateral delta-wave activity was noted in the electroencephalogram during the period when misnaming was observed. Frequencies ranged from 1 to 6 cps. The remaining patient had a normal record. Misnaming was never manifested by patients with only focal abnormalities of the electroencephalogram. The concurrent appearance of misnaming with other alterations in behavior and the pattern of electroencephalographic abnormality was shown in the case of a woman with metastatic neoplastic cerebral disease. On entering the hospital, she was depressed and well aware of her illness and left-sided weakness. Her electroencephalogram showed a focal abnormality on the right side. After a week she became euphoric, was disoriented for time of day, and denied illness. At the same time she first exhibited paraphasic responses, calling a penknife a "nail file" and referring to the examiner as Dr. "Weingarten," although she had previously given his name correctly. The electroencephalogram at this time revealed bilateral slow-

wave abnormalities. On the other hand, in patients with improvement in other manifestations of abnormal behavior the misnaming cleared concurrently.

In six patients with the severest behavior disturbances, condensations and apparent neologisms were noted. A patient with a tumor of the third ventricle (J. P.), whose case has been reported previously,[1a] said he had been a "bombigator" in the air force, the term apparently being a condensation of "bombardier" and "navigator." A girl with encephalitis, in the course of which she showed pronounced sexual erethism, called a syringe a "hermethisiac." Language disturbance was shown not only in the misnaming of objects, persons and places, but also in other forms. Some patients used phrases with obscure metaphorical content. One man described the doctors as "gathering information up to and including inventory." Another patient, when asked where she had been, replied, "Roaming around and then came back to the yampapa; we didn't splash in anyone else's territory."

In the present series of patients, the type of naming difficulties differed in certain consistent respects from that noted in aphasic patients. Words were not garbled, and the rhythm of speech was normal. Perseveration was not present. The patient did not appear to be aware of any errors in his speech, and when errors were pointed out by the examiner there was no evident anxiety, as in most aphasic patients. Likewise, attempts at correction did not help, in that the patient later in the examination would make the same or similar errors. Whereas the incorrect names given by aphasic patients were either apparently unrelated or related only in terms of the sound of the word, the paraphasic response, as mentioned previously, was related to a structural or functional aspect of the object. Spelling and reading were generally performed well.

When a paraphasic response was given, the patient was asked to demonstrate or state the use of the object. In some instances the function assigned was the proper one, despite the misnaming, but in patients with the severer disturbances the action demonstrated was consonant with the paraphasic response. Thus, one patient called the thermometer a "drinking tube" and actually attempted to use it as a straw. Another patient called a thermometer a "nail" and went through the motions of hammering on it. In several instances the disturbed perception was spontaneously shown in "bizarre" acts. An early symptom of a woman with a neoplasm of the third ventricle was her serving a cake with grapes instead of cherries on it. One of the patients with a subarachnoid hemorrhage defecated into a utility hopper and argued with the nurse who tried to convince her that it was not a toilet.

Perception was further tested by observing the patients' reaction to the double simultaneous cutaneous stimulation, according to the technique reintroduced by Bender.[3] In 17 cases tactile stimuli, usually the examiner's fingers, were applied simultaneously to the patient's cheek and extremities in various paired combinations. In 16 of these cases the patient either did not perceive the stimulus applied to the extremity (extinction) or displaced it to another part of his body or extracorporeally.

3. Bender, M. B.; Fink, M., and Green, M.: Patterns in Perception on Simultaneous Tests of Face and Hand, Tr. Am. Neurol. A. **75**:250-252, 1950.

COMMENT

Although paraphasia is ordinarily regarded as a type of receptive aphasia, it is difficult to relate the findings in the present study to any of the various concepts of aphasia. While aphasia frequently occurs with a unilateral lesion in the dominant hemisphere associated with a focal electroencephalographic abnormality,[4] in our patients paraphasia was observed almost always with bilateral electroencephalographic abnormalities produced by single or multiple lesions. When paraphasia occurred with a single lesion and normal intracranial pressure, the lesion was so situated that it crossed the midline in the region of the third ventricle. With increased intracranial pressure or bleeding into the cerebrospinal fluid, paraphasia was present with lesions anywhere in the brain. A fairly rapidly progressing pathologic process was necessary, so that misnaming was seen in cases of tumor and hemorrhage rather than in cases of chronic degenerative or demyelinating disease.

Apart from the question of anatomical localization, there are significant points of differentiation between the observed behavior of patients with misnaming and that of patients with aphasia. Unlike the disorder shown by aphasic patients, the words of patients with misnaming were not garbled, their rhythm of speech was normal; perseveration was not present; there was no awareness of errors; correction led to no improvement; spelling and reading were generally unimpaired, and there was no conspicuous anxiety.

Besides the phenomena observed in aphasic patients but not in our patients with misnaming, certain associated changes in behavior were shown by all the paraphasic patients which were not ordinarily found in aphasia. These included disorientation, anosognosia and other delusions, confabulations, change in psychomotor activity, mood changes, hallucinations, and incontinence. There appeared to be a marked change in the patient's relation to the environment in that certain aspects were perceived while others were rigidly excluded. This type of selective perception was seen not only in the paraphasic naming in terms of some single feature of structure and/or function of the object perceived, but also in the mechanism of the anosognosia and disorientation. Thus, a patient, though she named the hospital correctly, insisted that it was only one block away from her home because she believed that she recognized a familiar building when she looked out the window.

The altered perceptual organization in the paraphasic patients was also indicated by their response to the simultaneous application of two cutaneous stimuli, in which one stimulus was either completely excluded or displaced to another part of the body. Bender, Fink, and Green [3] found that, in contrast to such patients, persons with aphasia did not show this type of perceptual alteration.

From the way in which it is manifested, paraphasia evidently represents a change in both symbolic and perceptual function. Paterson and Zangwill [5] described paraphasia in cases of head injury with disorientation and likewise regarded it as a dis-

4. Weinstein, E. A.; Kahn, R. L., and Strauss, H.: Correlation of Clinical and EEG Abnormalities in Tumors and Vascular Disease of the Brain, Tr. Am. Neurol. A. **75**:277-278, 1950.

5. Paterson, A., and Zangwill, O. L.: Recovery of Spatial Orientation in the Post-Traumatic Confusional State, Brain **67**:54-68, 1944. Paterson, A.: Emotional and Cognitive Changes in the Post-Traumatic Confusional State, Lancet **243**:717-720, 1942.

turbance in perception. Both Hughlings Jackson [6] and Head [7] described cases of "imperception," the protocols of which reveal paraphasic responses. Jackson's patient was a woman with a glioma of the right temporal lobe who made errors in recognition of places, persons, and objects. In her paraphasic responses, she called the strings on the nurse's cap "long tails," a penny a "shilling," and a new penny a "sovereign." Head described a patient with vascular disease who had a succession of strokes. She called a pocket knife a "purse" because "it was something to open" and a riding boot a "knapsack" because "it belonged to soldiers." Head stressed that his patients had progressive and diffuse lesions of the brain.

We [1] have previously pointed out that in the patterns of anosognosia and disorientation the selective perception of the environmental data is not fortuitous. It was significant that with many of the patients misnaming occurred only with objects, persons, and places concerned with the illness. Curran and Schilder,[8] in describing three cases of paraphasia, likewise pointed out that the choice of words is connected with the patient's own experience. Thus, in calling the interviewing physician a "lawyer," the patient reacts only to one aspect of the relationship and eliminates that feature having to do with his illness. Recent experiments on "social perception" have demonstrated that in normal persons internal factors, such as motivation and expectancy, may likewise influence perception.[9] In normal persons special conditions, such as decreasing the time of exposure of the stimulus (tachistoscopy) or increasing the ambiguity of the stimulus, are usually necessary to facilitate the motivational aspects of perception.

Most authors agree with Head's definition of aphasia as a defect in symbolic formulation and expression. However, as previously shown by Goldstein,[10] the words used by paraphasic patients have a high degree of symbolic content. It may be helpful, in appreciating the difference between this paraphasic kind of misnaming and aphasia, to use Sapir's [11] classification of the symbolic functions of language as of two kinds, referential and experiential. Referential symbolism embraces such forms as oral speech, writing, mathematical notations, and other devices which are agreed upon as economical devices for purposes of communication and reference. Aphasia can be considered a defect in symbolic function in which the difficulty lies in associating an object with the referrent symbol for that object. In paraphasic misnaming, on the other hand, the name of the object seems to serve as the vehicle for some individual experience or emotion. The name given to the

6. Jackson, J. H.: Selected Writings of John Hughlings Jackson: Evolution and Dissolution of the Nervous System, Speech, Various Papers, Addresses and Lectures, Edited by James Taylor and others, London, Hodder & Stoughton, Ltd., 1932, Vol. 2, pp. 146-152.

7. Head, H.: Aphasia and Kindred Disorders of Speech, Cambridge, Cambridge University Press, 1926, Vol. 1, pp. 103-115.

8. Curran, F. J., and Schilder, P.: Paraphasic Signs in Diffuse Lesions of the Brain, J. Nerv. & Ment. Dis. **82**:613-636, 1935.

9. Bruner, J. S., and Postman, L.: An Approach to Social Perception, in Dennis, W., Editor, Current Trends in Social Psychology, Pittsburgh, University of Pittsburgh Press, 1948, pp. 71-118.

10. Goldstein, K.: Language and Language Disturbances: Aphasic Symptom Complexes and Their Significance for Medicine and Theory of Language, New York, Grune & Stratton, Inc., 1948.

11. Sapir, E.: Symbolism, in Encyclopedia of the Social Sciences, E. R. A. Seligman, Editor, New York, The Macmillan Company, 1934, Vol. 14, pp. 492-495.

object serves not primarily to communicate with others, but to express the person's own feelings and to resolve his own anxiety. It is not that the patient has lost the ability to use the referential symbol, but that there is a drive and need to substitute the experiential symbol. Thus, one patient, when asked to name the side rail on her bed, said "I call it a bed post, but it could be called a railing."

Although paraphasia [12] occurs with organic brain disease, it cannot be considered to represent a specific defect in function, any more than can the patient's confabulations or his euphoric or paranoid mood. Pick,[13] noting paraphasia in normal persons, attributed it to a lapse in "attention." Freud [14] observed a similarity between mistakes in speech and paraphasia. We have been impressed by the paraphasic quality of slang and nicknames. The use of metonyms in the speech of schizophrenic patients [15] also appears to be similar to paraphasic phenomena. The resemblance of the amnestic-confabulatory syndrome, of which paraphasic misnaming is a part, to dreams has frequently been stressed. Displacements, distortions, and condensations appear in each, and the use of words and names as experiential symbols differs from the conventional referential usage of the waking state. Paraphasic misnaming is often elicited from patients without brain disease while under the influence of amobarbital sodium,[16] although such patients do not show any predilection for misnaming hospital objects.

It appears that the pathologic process in the brain does not in itself produce this type of naming disturbance, but brings out a normally occurring mechanism. Thus, the amount of paraphasia shown by patients with similar lesions may vary a great deal. The lesion makes possible the continuation of a perceptual and symbolic interrelationship, not unlike that which is seen under the conditions of sleep. In this, the misnaming, like anosognosia and disorientation, may be seen as an exaggeration of a normal pattern of behavior.

SUMMARY

In 30 patients with organic brain disease a type of misnaming was observed in which objects, persons, and places were named in terms of only certain aspects of their structure or function. The substituted names were most frequently used with objects bearing a relation to the patient's illness.

The misnaming never occurred as an isolated phenomenon but was associated with other changes in behavior, such as disorientation, denial of illness and other delusions, and mood changes.

12. The term "paraphasia" is a poor one to describe the observed misnaming phenomena. It would be desirable to employ a term which would differentiate it from aphasia, indicating the altered perceptual, as well as symbolic, behavior.

13. Pick, A., and Thiele, R.: Aphasie, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, Vol. 15, Pt. 2, pp. 1416-1524.

14. Freud, S.: Psychopathology of Everyday Life, in The Basic Writings of Sigmund Freud, translated from the German and edited by A. A. Brill, New York, Random House, Inc., 1938, p. 69.

15. Cameron, N.: Experimental Analysis of Schizophrenic Thinking, in Kasanin, J. S., Editor, Language and Thought in Schizophrenia, Berkeley, Calif., University of California Press, 1946.

16. Unpublished observation of the authors.

In 16 of 17 patients extinction and displacement of one of two simultaneously applied cutaneous stimuli could be observed. This was regarded as further evidence of a generalized alteration of perception.

In 25 of 26 patients the electroencephalogram showed bilateral diffuse delta-wave activity.

The intracranial pathology consisted mainly of deeply situated or bilateral tumors and aneurysms with subarachnoid hemorrhage.

Though called verbal paraphasia, it is believed that this type of misnaming should not be classed as an aphasic disorder. It is not explicable as a defect in symbolic formulation or expression associated with a lesion of the dominant hemisphere. It is, rather, a manifestation of a more general change in behavior, involving altered patterns of perception and motivational factors.

RESULTS OF TREATMENT OF SCHIZOPHRENIA IN A STATE HOSPITAL

Changing Trends Since Advent of Electroshock Therapy

GEORGE E. CURRIER, M.D.
CATHERINE CULLINAN, M.D.
AND
DAVID ROTHSCHILD, M.D.
WORCESTER, MASS.

THE TREATMENT of schizophrenic psychoses has always presented a challenge to psychiatry. Attitudes toward their treatment have changed from time to time, depending to some extent on prevailing conceptions of the nature of these disorders. The traditions handed down from the teachings of Kraepelin tended toward a highly pessimistic outlook. In recent years more optimistic views have commonly been expressed. One of the factors contributing to this change has apparently been the enthusiasm associated with the introduction of the shock therapies. These new procedures cannot be regarded as panaceas, but they have undoubtedly tended to minimize fatalistic attitudes and stimulate more active therapeutic efforts in a variety of directions.

One may properly ask whether a more optimistic attitude is justified by any measurably greater success of treatment in recent years, and, if so, whether credit should be given partially or fully to the shock therapies. Unfortunately, reliable comparisons are difficult to make. There are many variables which may affect the results. Rees [1] has discussed many of the obstacles in the way of an attempt to assess scientifically any new method of treatment in psychiatry. He pointed out that the difficulties are greatest in attempting to deal with data from various hospitals because of the varying criteria used in assessing the clinical status. Nevertheless, the whole subject seems important enough to warrant careful investigation. Within the same hospital it may be possible to overcome the difficulties. Controls of some sort can be established and allowance made for many of the factors which influence the outcome, so that reliable comparisons of present-day and past results may perhaps be made.

MATERIAL AND METHOD

The present study was undertaken in an attempt to make such comparisons, using for evaluation of present-day results a period when electroshock therapy was freely employed. The period chosen was the year from July 1, 1946, to June 30, 1947, during which electroshock was the only type of shock therapy given. For purposes of comparison with results obtained prior to the advent of electroshock therapy, data from the years 1934 and 1935 were scrutinized. It was necessary to use a two-year period to obtain a group of approximately equal size, owing to the smaller number of admissions during those years. The study was limited to female patients. There were 112 patients in the 1946-1947 group and 119 in the group for 1934 and

From the Clinical Services of the Worcester State Hospital.

1. Rees, L.: Electronarcosis in the Treatment of Schizophrenia, J. Ment. Sc. **95**:625, 1949.

1935. All female patients admitted during the above-mentioned years and with a condition diagnosed as schizophrenic were used, with the exception of 49, who were excluded because of inadequate records or early transfer to other hospitals or because they were transferred to the Worcester State Hospital from other state hospitals for administrative reasons and thus did not represent the usual flow of admissions from the community.

The results of treatment were determined from 13 months to 3 years after the date of admission. When the patient was discharged after brief hospitalization, her condition was evaluated one year after her return to the community. The status of all patients was evaluated in terms not only of disposition, but also of degrees of improvement, as judged by a scrutiny of the case records, supplemented in the more recent period by personal observations on most of the patients. The clinical estimation of the level of improvement is admittedly inexact, but it is probably a better measure of the real results of treatment than the circumstance that the patient is in or out of the hospital, since the disposition in a considerable number of cases depends on the facilities for supervision in the community rather than on the actual condition of the patient. Therefore, the degree of improvement will be stressed, and the patient's status will be described under the following headings:

Much improved: Under this term are included those patients who were able to make a good social and work adjustment outside the hospital under conditions equaling or closely approximating their prepsychotic level.

TABLE 1.—*Results of Treatment of Schizophrenia in Female Patients Admitted During the Years 1934 and 1935 and 1946-1947*

	1934-1935		July 1, 1946-June 30, 1947	
	Number of Patients	Percentage	Number of Patients	Percentage
Discharged	27	22.5	57	51
On visit	8	6.5	12	10.7
Family care	7	6	0	0
Still in hospital	70	59	41	36.5
Dead	7	6	2	1.8
Totals	119	100	112	100
Improved or much improved	27	22.5	67	60

Improved: Under this term are included those patients who had decidedly improved; they showed some psychotic residuals but were able to function in the community or in the hospital with a minimum of supervision.

Slightly improved: Under this term are included those patients who were still overtly psychotic but were making a somewhat better adjustment within the hospital or at home under close supervision.

Unimproved: Under this term are included the patients whose condition was unchanged or worse.

For purposes of convenience in evaluating the results, the patients whose condition was much improved and those who showed improvement were included together, thus providing a figure which, for practical purposes, can be regarded as representing a satisfactory outcome.

RESULTS

Over-All Results of Treatment.—Table 1 shows the over-all results for the two periods under review. The figures clearly indicate better results in the 1946-1947 than in the 1934-1935 period, whether one uses as the criterion the degree of improvement or the disposition of the patient. Thus, 60% of the 1946-1947 group were improved or much improved, as compared with 22.5% for the 1934-1935 group. This difference was highly significant statistically, the P value of the χ^2 test being 0.001. Under the category of "much improved," which represents the most complete remissions, were classified 31% of the 1946-1947 group and only 7% of

the 1934-1935 group. For the category of "unimproved," which represents the complete failures of treatment, the figures were 20% for the 1946-1947 period and 48% for 1934 and 1935. At the end of the follow-up period, 65% of the patients in the 1934-1935 group were still in the hospital or were dead, as compared with 38.3% of the 1946-1947 group.

While the number of deaths was too small to provide data of definite significance, it is interesting to note that 7 of the 119 patients in the earlier group died during the follow-up period, as compared with 2 of the 112 patients in the 1946-1947 group.

In order to determine why the results were significantly better in 1946-1947 than in 1934 and 1935, a more detailed analysis of the data is necessary, with special attention to the results of electroshock therapy and to any other factors which might affect the outcome and, at the same time, differ in the two groups.

Results of Treatment, With and Without Electroshock, in 1946-1947 Period.—Of the 112 patients admitted during the 1946-1947 period, 75 received electroshock therapy, given in the conventional manner, as a rule in courses up to 20 treatments.

TABLE 2.—*Results of Treatment with Electroshock in Female Schizophrenic Patients Admitted During 1946*

Type of Schizophrenia	Total No. of Cases	Status				Number of Patients Out of Hospital	Percentage of Improved and Much Improved Patients
		Unimproved	Slightly Improved	Improved	Much Improved		
Catatonic	22	2	1	6	13	19	86
Other types	28*	2	3	11	11	20	79
Paranoid	14	4	3	3	4	8	50
Hebephrenic	9	2	0	4	3	7	78
Simple	2	1	0	1	0	0	50
Totals	75	11	7	25	31	54	75

* This number includes one patient who died during the period under study and was therefore not classified in terms of degree of improvement.

In the great majority of cases only one course of treatment was administered. The data are presented in Table 2.

As might be expected, the best results were obtained in catatonic patients and in patients with schizoaffective disturbances classified as "other types" of schizophrenia. At the same time, patients with the paranoid and, especially, the hebephrenic type of schizophrenia did surprisingly well with electroshock therapy, though the numbers involved were probably too small to be of definite significance.

The results for the 37 patients who did not receive electroshock are presented in Table 3. The status of only 30% of these patients was improved or much improved, as compared with 75% of the group receiving electroshock therapy. This difference was highly significant, the χ-square test giving a P value which would occur less than 0.1% of the time by chance alone. On the other hand, the percentage of patients in Table 3 whose condition was improved or much improved is not significantly different than the corresponding percentage for the 1934-1935 group (Table 1).

The superior results in the patients receiving electroshock were clearly responsible for the greater success attained in 1946-1947 than in 1934 and 1935. However, without further analysis of the data, full or partial credit for this cannot be

attributed to the shock treatment, since it was not administered routinely. For the most part, it was given in those cases in which, according to general experience, the prognosis was likely to be good. Thus, it is possible that a favorable selection of patients, rather than the treatment itself, was responsible for a favorable outcome in 86% of cases of catatonia and in 79% of cases of the "other types" treated with electroshock (Table 2). These two types of schizophrenia showed significantly better results than did the other subtypes in the total 1946-1947 group. However, the poorer results in 1934 and 1935 could not be attributed to a different and more unfavorable distribution of the cases among the various subtypes, for the differences in this respect between the two periods under review were only minor, and of no statistical significance.

Factors in Outcome of Treatment.—There are, of course, other factors which influence the outcome, and for an evaluation of their effects it is necessary to determine their frequency of occurrence in each group. A study of our material indicated that the following variables appeared to have a statistically significant relation to

TABLE 3.—*Results of Treatment, Without Electroshock, in Female Schizophrenic Patients Admitted During the 1946-1947 Period*

Type of Schizophrenia	Total No. of Patients	Status				Number of Patients Out of Hospital	Percentage of Improved and Much Improved Patients
		Unimproved	Slightly Improved	Improved	Much Improved		
Catatonic	3	2	1	0	0	1	0
Other types	10*	3	1	1	4	6	50
Paranoid	20	6	9	5	0	7	25
Hebephrenic	4	3	0	1	0	1	25
Simple	0	0	0	0	0	0	0
Totals	37	14	11	7	4	15	30

* This number includes one patient who died during the period under study and was therefore not classified in terms of degree of improvement.

the results of treatment: age on admission, duration of the illness prior to hospitalization, and type of onset. Each of these factors disclosed differences, represented by P values in the χ^2 test of 0.1%. Finally, a study of matched cases from the two periods under review was made in order to determine whether or not a combination of the foregoing variables might be responsible for the differences in the results of treatment. These points will be discussed in the following paragraphs.

Age on Admission[2]: It was found that better results occurred in patients under 40 years of age on admission than in those over 40, as indicated in Table 4. This trend was noted in all groups, although it was most pronounced in the patients treated with electroshock and least noticeable in the patients belonging to the 1934-1935 period.

The fact that the group treated with electroshock contained by far the largest proportion of patients under the age of 40 raises the question whether this age distribution, rather than the shock treatment, was responsible for the more favorable results in that group. A scrutiny of Table 4 indicates that the age factor by itself cannot account for the differences, since the patients under 40 who did not

2. The lower age range was limited to 16 years, since patients below that age are not admitted to the hospital.

receive electroshock showed much less favorable results than those who did. The observations suggest that the preponderance of younger patients in the group receiving electroshock contributes to, but does not wholly explain, the success of that form of treatment.

Duration of Illness Prior to Hospitalization: The data are presented in Table 5. As would be expected, the results were most favorable in patients with illnesses of six-months' duration or less, and they were progressively less satisfactory as the

TABLE 4.—*Results of Treatment According to Age on Admission*

Age on Admission	Number of Patients	Number of Improved and Much Improved Patients	Percentage of Improved and Much Improved Patients
Under 40 yr.			
1946-1947 group with electroshock	65	52	80
1946-1947 group without electroshock	13	7	54
1934-1935 group	66	18	27
Over 40 yr.			
1946-1947 group with electroshock	10	4	40
1946-1947 group without electroshock	24	4	17
1934-1935 group	53	9	17

TABLE 5.—*Results of Treatment According to Duration of Illness Prior to Hospitalization*

Duration of Illness Prior to Hospitalization	Number of Patients	Number of Improved and Much Improved Patients	Percentage of Improved and Much Improved Patients
6 mo. or less			
1946-1947 group with electroshock	46	43	93
1946-1947 group without electroshock	9	6	67
1934-1935 group	36	18	50
7 mo. to 1 yr.			
1946-1947 group with electroshock	8	6	75
1946-1947 group without electroshock	2	0	0
1934-1935 group	10	2	20
1 yr. or more			
1946-1947 group with electroshock	21	7	33
1946-1947 group without electroshock	26	5	19
1934-1935 group	73	7	10

duration of the illness became greater. In spite of the small size of the groups, this trend was consistent except in one, which contained only two cases (Table 5). At the same time, the patients treated with electroshock showed higher rates of improvement than did the other groups with illnesses of similar duration. Thus, the more favorable results associated with electroshock therapy cannot be due entirely to differences in the duration of the illness.

Type of Onset: All patients were classified in two groups: those with an acute and those with a gradual onset of the psychosis. The data are presented in Table 6. They reveal the expected effect, namely, a more favorable outcome in the patients with acute onset whenever similarly treated groups are compared. At the same time, the highest proportion of good results was observed in the patients treated

with electroshock, though the greatest difference in the figures occurred among the three groups of patients with a psychosis of gradual onset. Here, too, the observations suggest that the type of onset is an important factor in the outcome, but that it cannot wholly account for the superior results associated with electroshock therapy.

Comparison of Matched Cases: The cases of all patients admitted during the 1946-1947 period were compared with those of all admissions in 1934 and 1935 in order to obtain matched pairs which showed similarity in the following variables: type of schizophrenia, age on admission, duration of illness prior to hospitalizaton, and type of onset. The age on admission could not always be matched to the

TABLE 6.—*Results of Treatment According to Type of Onset*

	Number of Patients	Number of Improved and Much Improved Patients	Percentage of Improved and Much Improved Patients
Acute Onset			
1946-1947 group with electroshock	29	26	90
1946-1947 group without electroshock	6	5	83
1934-1935 group	20	13	65
Gradual Onset			
1946-1947 group with electroshock	46	30	65
1946-1947 group without electroshock	31	6	19
1934-1935 group	99	14	14

TABLE 7.—*Comparison of Results in Matched Patients*

		Status				Percentage of Patients Improved and Much Improved
Matched Patients	Number of Patients	Unimproved	Slightly Improved	Improved	Much Improved	
With electroshock						
1946-1947 group	36	6	5	11	14	70
1934-1935 group	36	16	6	8	6	39
Without electroshock						
1946-1947 group	19	7	8	2	2	21
1934-1935 group	19	10	7	2	0	10
All matched patients 1946-1947	55	13	13	13	16	53
All matched patients 1934-1935	55	26	13	10	6	29

identical year, but in most instances the differences were not greater than one or two years. With respect to the duration of the illness, the cases in the two periods were not identical, but they were paired according to the three categories in Table 5, care being taken to avoid too great differences in those cases in which the illnesses were of more than one-year's duration. Even with these limitations, the groups can be regarded as very closely comparable. The number that could be matched in this manner was 55 cases in each of the two periods under review. Of the 55 cases in the 1946-1947 period, electroshock was given in 36.

The observations are presented in Table 7. In the matched cases, the superiority of the results in the whole 1946-1947 group was less pronounced than that in the unmatched cases, owing to a slight drop (from 60 to 53%) in the figures for the 1946-1947 period and a slight rise (from 22.5 to 29%) in the figures for 1934 and

1935. This difference was still significant, the P value of the χ^2 test being 0.6%. A similar phenomenon was noted when the 36 patients treated with electroshock in the 1946-1947 period were matched with 36 patients from the 1934-1935 series, 70% of the former and 39% of the latter showing good results. The comparable figures were 75% for all patients receiving electroshock and only 22.5% for the whole 1934-1935 group. Thus, the superiority of the results associated with electroshock therapy has become less pronounced in the matched patients, but the difference remains significant statistically, the P value of the χ^2 test being 0.1%.

It has already been noted that there was a preponderance of favorable prognostic factors in the whole group receiving electroshock and that the better results in that group could not be explained by a study of each factor individually. The possibility that some combination of these factors might be primarily responsible for the differences can now be dismissed in view of the observations on the groups who were matched in order to eliminate any such combination. On the one hand, the narrowing in the margin of superiority of electroshock treatment in the matched groups indicates that a preponderance of favorable factors definitely contributed to the over-all success of shock therapy. On the other hand, the margin of superiority was still significant after the effects of these variables were discounted, so that they fail to account for the major part of the disparity between the results obtained with and without electroshock.

COMMENT

According to our observations, the results of treatment were decidedly better in female schizophrenic patients admitted during the 1946-1947 period than in similar patients admitted during 1934 and 1935. The difference was due to the superior results obtained in the members of the 1946-1947 group who received electroshock therapy. Thus, 75% of these patients were improved or much improved at the end of the follow-up period, as compared with 30% of the other patients in the 1946-1947 series and 22.5% of the series of 1934 and 1935.

In attempting to evaluate the foregoing data, it must be remembered that a total hospital program includes many interpersonal therapeutic factors, which may differ in the various groups. Unfortunately, such influences cannot be assessed adequately. It is impossible to compare the present activities with a treatment program carried out many years ago with different personnel. Nevertheless, it should be noted than in 1934 and 1935 the Worcester State Hospital was an active teaching and research center, so that it would be incorrect to assume that the unfavorable comparison with the 1946-1947 results was due to an inactive staff.

Apart from these considerations, the observations suggest that much of the credit for the more favorable results in the 1946-1947 period should be attributed to the use of electroshock therapy. This conclusion receives support from the data on the matched cases (Table 7) and from the figures in Tables 4, 5, and 6, which indicate that, no matter what type of grouping is studied, electroshock therapy has the effect of raising the percentage of satisfactory results. While the number of cases, particularly in some categories, was not large, the results were consistent enough to suggest that they were valid.

At the same time, part of the credit for better results in the patients receiving electroshock was due to the circumstance that such treatment was given to a a selected group in which there was a preponderance of favorable prognostic

factors. A number of influences of this type were disclosed by the present study. These factors have already been discussed. They are well known with the exception of one, namely, the age on admission, which seems to have received little attention in the literature. Our figures (Table 4) strongly suggest that the prognosis is better for patients under 40 than for those over 40 years of age on admission.

A number of other variables showed trends which were suggestive, though below the level of statistical significance, so that only brief mention of them will be made. Patients who had one or more periods of hospitalization, with return to the community prior to the present study, showed a greater tendency toward improvement than the patients who had no previous attacks. Trends toward a more favorable outcome were noted in married patients, as compared with other patients, and in patients whose illness showed obvious precipitating factors. Patients with low average intelligence tended to exhibit slightly better results than those with high average or superior intelligence. The results were somewhat better, also, in patients with a history of mental illness in the immediate family than in patients without such a family history.

In general, our results with electroshock seem more favorable than many of those reported in the literature, but the differences could well be due to differences in the composition of the case material, as well as in standards of diagnosis and evaluation of end-results. Finiefs [3] found that 39% of 82 patients receiving convulsive-shock treatment were improved or much improved, and Rees [1] reported 8% of 72 patients as recovered and 24% as improved and discharged. These figures are much lower than our results for roughly comparable categories. According to Malzberg,[4] the condition of 38% of 249 female patients treated with electroshock was unimproved or worse. This may be compared with our figure of 25% for the patients with no and with slight improvement in the group treated with electroshock. On the other hand, our observation that 93% of the patients ill for six months or less were improved or much improved is similar to the findings of Kalinowsky and Worthing,[5] who stated that 67.4% of their patients with illnesses of less than six months' duration were recovered or much improved, and 21.7% were improved. Gottlieb and Huston [6] reported complete and social recovery in 45% of their patients treated with electroshock. This corresponds closely with our figure of 41% for the patients whose condition was much improved, a category probably similar to their complete and social recovery.

The present observations should not be taken as an indication that other methods of therapy may or may not be equal or superior to electroshock. What they do indicate is that with methods readily available, in this instance, electroshock, the results of treatment in schizophrenic patients are distinctly better now than they were only 15 years ago within the same hospital.

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3. Finiefs, L. A.: Results of Treatment of 1,000 Cases of Schizophrenia, J. Ment. Sc. **94**:575, 1948.

4. Malzberg, B.: Outcome of Electric Shock Therapy in the New York Civil State Hospitals, Psychiat. Quart. **17**:154, 1943.

5. Kalinowsky, L. B., and Worthing, H. J.: Results with Electric Convulsive Therapy in 200 Cases of Schizophrenia, Psychiat. Quart. **17**:144, 1943.

6. Gottlieb, J. S., and Huston, P. E.: Treatment of Schizophrenia: A Comparison of Three Methods: Brief Psychotherapy, Insulin Coma and Electric Shock, J. Nerv. & Ment. Dis. **113**:237 (March) 1951.

Finally, attention should be called to a striking and highly desirable alteration in the nature of the admissions during the 1946-1947 period as compared with those during 1934 and 1935. Patients under 40, patients with an acute onset, and, especially, patients with brief illnesses formed a much larger proportion of the admissions in the later than in the earlier period. Since there were no noteworthy changes in the policies of admission during these periods, one may assume that in the past 10 or 15 years the community has become more aware of the importance of early hospitalization and treatment for schizophrenic patients. One may wonder whether the more optimistic attitudes now prevalent in psychiatry have helped to produce this alteration, which, in its turn, obviously increases the likelihood of successful treatment. There are many factors, apart from the treatment itself, which may favorably influence the outcome, and it is possible that a combination of such favorable factors plus electroshock therapy may have cumulative beneficial effects.

SUMMARY

The results of treatment in 112 female schizophrenic patients admitted during the year July 1, 1946, to June 30, 1947, were compared, after a follow-up period of 13 months to 3 years, with the results in 119 female patients admitted during 1934 and 1935. Of the 112 patients admitted in 1946-1947, 75 received one or more courses of electroconvulsive therapy.

The over-all results were significantly better in the 1946-1947 period, 60% of the patients being improved or much improved, as compared with 22.5% of the patients admitted during 1934 and 1935. This difference was due to superior results obtained in those members of the 1946-1947 group who received electroshock therapy; 75% of these patients were improved or much improved, as compared with 30% of the untreated patients in the same series.

A study was made of the following variables which were found to influence the outcome significantly: subtype of schizophrenia, age on admission, type of onset, and duration of illness prior to hospitalization. Also, cases were matched from the two periods under review in order to determine whether or not a combination of the foregoing factors might be responsible for the differences in the results of treatment.

An analysis of the data suggested that the more successful results observed in the group receiving electroshock therapy were due in large part to the shock treatment itself, but contributing to its success was a preponderance of favorable prognostic factors which were present in the members of this group.

The observations suggested that in the past 10 or 15 years the community has become more aware of the importance of early hospitalization and treatment for schizophrenic patients.

MENINGOCOCCIC MENINGITIS

Incidence of Residua Following Serum, Sulfonamide, and Sulfonamide-Penicillin Therapy

ALEXANDER T. ROSS, M.D.
INDIANAPOLIS

PRIOR to the use of specific antimeningococcic serum in treatment of patients by Flexner and Jobling [1] in 1908, the therapy of meningococcic meningitis was symptomatic and was attended by a mortality rate of 20 to 90%. From then until the advent of chemotherapy, routine management consisted of frequent spinal drainage, adequate supportive care, and the injection of serum intrathecally, intravenously, or intramuscularly, or in combination of these routes. These procedures reduced the mortality rate to a range of 15 to 50%. As experience grew, the use of intrathecal therapy and frequent drainage was decried (Hoyne [2]; Tripoli [3]), the intramuscular and intravenous routes being advocated.

In 1936 the sulfonamides came into general use and in one form or another have supplanted serum therapy. Varying figures have been given for the relative efficacy of the different members of the sulfonamide group, but in general sulfadiazine is most favored because of its slighter tendency to produce side-reactions and its greater diffusibility into the spinal fluid. Zeller and his associates [4] used a combination of sulfadiazine and sulfamerazine and concluded that the advantages over administration of a single drug gained by this method were outweighed by the incidence of undesirable effects, such as fever, rash, and conjunctivitis.

Since 1944 penicillin has been utilized, either as the sole therapeutic agent or as an adjunct to the sulfonamides. Different opinions of its value also have been expressed. Thus, Hoyne and Brown [5] reported a fatality rate of 14% with sulfadiazine, 12.8% with sulfathiazole, 13.3% with sulfamerazine, and 25% with sulfapyridine, as against 26.2% with a combination of sulfonamides and penicillin. Rhoads [6] found a mortality rate of 10.5% with the use of sulfonamides alone, 14.3%

From the Department of Neuropsychiatry, Indiana University Medical Center, and the Indianapolis General Hospital.

Read before the Section on Nervous and Mental Diseases, at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, N. J., June 14, 1951.

1. Flexner, S., and Jobling, J. W.: Serum Treatment of Epidemic Cerebro-Spinal Meningitis, J. Exper. Med. **10**:141, 1908.

2. Hoyne, A. L.: Epidemic Meningitis, J. A. M. A. **115**:1852 (Nov. 30) 1940.

3. Tripoli, C. J.: Treatment of Epidemic Meningitis (Cerebrospinal Fever): Results in 115 Cases with Special Reference to the Fallacy of Intraspinal Therapy, South. M. J. **35**:472 (May) 1942.

4. Zeller, W. W.; Hirsh, H. L.; Sweet, L. K., and Dowling, H. F.: Treatment of Meningitis with Sulfadiazine and Sulfamerazine, J. A. M. A. **136**:8 (Jan. 3) 1948.

5. Hoyne, A. L., and Brown, R. H.: Seven Hundred and Twenty-Seven Meningococcic Cases: An Analysis, Ann. Int. Med. **28**:248 (Feb.) 1948.

6. Rhoads, P. S.: Clinical Analysis of 550 Cases of Bacterial Meningitis, Am. Pract. **1**:305 (Feb.) 1947.

when sulfonamides were combined with penicillin, and 22.2% with penicillin alone. Brainerd and Bradley [7] reported a mortality rate of 12.2% with sulfonamides alone and 4.8% when penicillin was added. The injection of penicillin intrathecally was advocated for some time; then doubts of the advisability of this technique were raised, being considered that the drug so administered was a further irritant to already damaged meninges and liable to produce adhesions and neural damage, owing to its concentration in a slowly circulating medium.[8] This matter is not yet settled, but the general attitude seems to be respect for the delicacy of the meninges and the nervous system.

Table 1 presents some of the mortality figures reported for the different therapies.

Infection by the Meningococcus produces more than purulent meningitis; acute encephalomyelitis may occur, with widespread damage to neurons, disseminated

TABLE 1.—*Reported Mortality Percentages for Various Therapies of Meningococcic Meningitis*

	Serum	Serum and Sulfonamides	Sulfonamides	Sulfonamides and Penicillin	Penicillin
McLean and Caffey *	49	....	....	....	....
Borovsky †	48.9	....	....	....	....
Banks ‡	16	11.8	6.2	....	....
Hodes and Strong §	....	....	10.9	....	....
Harries ‖	42	19	8.6	....	....
Jubb ¶	....	13.8	9.2	....	....
Beeson and Westerman #	....	18.8	14.3	....	....
Rosenberg and Arling **	....	....	....	....	1.3
Sweet and others ††	....	....	10.1	....	....
Davis and others ‡‡	....	13.2	....	....	....
Brainerd and Bradley [7]	....	....	12.2	4.8	....
Rhoads [6]	....	....	4.2-12.9	14.3	22.2
Hoyne and Brown [5]	....	....	12.8-25.0	26.2	....

* McLean, S., and Caffey, J. P.: J. A. M. A. **87**:91 (July 10) 1926.
† Borovsky, M. P.: Am. J. M. Sc. **179**:82, 1930.
‡ Banks, H. S.: Lancet **2**:7 (July 2) 1938.
§ Hodes, H. L., and Strong, P. S.: J. A. M. A. **119**:691 (June 27) 1942.
‖ Harries, J. E.: Brit. M. J. **2**:423 (Oct. 10) 1942.
¶ Jubb, A. A.: Brit. M. J. **1**:501 (April 24) 1943.
# Beeson, P. B., and Westerman, E.: Brit. M. J. **1**:497 (April 24) 1943.
** Rosenberg, D. H., and Arling, P. A.: J. A. M. A. **125**:1011 (Aug. 12) 1944.
†† Sweet, L. K.; Dumoff-Stanley, E., and Dowling, H. F.: Ann. Int. Med. **23**:338 (Sept.) 1945.
‡‡ Davis, J. H.; Morrow, W. J., and Toomey, J. A.: J. Pediat. **26**:455 (May) 1945.

capillary thromboses and hemorrhages, and edema and degenerative effects in the cortex and brain substance (Wertham [9]; Banks and McCartney [10]). Being systemic and of varying virulence, the infection may produce necrotic, exudative, embolic, toxic, and compressive effects in many sites. These complications occur early in the

7. Brainerd, H., and Bradley, E.: Treatment of Bacterial Meningitis with Penicillin, Sulfonamides, and Sera, California Med. **66**:57 (Feb.) 1947.

8. Reese, H. H., and Masten, M. G., in discussion on Editor's Note, The 1948 Year Book of Neurology, Psychiatry, and Neurosurgery, Chicago, The Year Book Publishers, 1948, p. 125. Hoyne, A. L.: The Acute Infectious Diseases, M. Clin. North America **31**:61 (Jan.) 1947. Wilson, G.; Rupp, C., and Wilson, W. W.: The Dangers of Intrathecal Medication, J. A. M. A. **140**:1076 (July 30) 1949.

9. Wertham, F.: The Cerebral Lesions in Purulent Meningitis, Arch. Neurol. & Psychiat. **26**:549 (Sept.) 1931.

10. Banks, H. S., and McCartney, J. E.: Meningococcal Encephalitis, Lancet **1**:219 (Feb. 14) 1942.

disease and may be fatal, transient, or followed by permanent residua. The Waterhouse-Friderichsen syndrome denotes an overwhelmingly toxic and highly fatal infection. Bennett [11] described a case of rapid death due to herniation of the cerebellum incidental to intracranial edema and congestion. Ocular complications include iridocyclitis, metastatic endophthalmitis with abscess formation in the vitreous, retinal detachment, papillitis, transient amaurosis, strabismus, and optic nerve atrophy.[12] Monoarticular or polyarticular purulent synovitis is not uncommon, but, fortunately, complete recovery is usual.[13]

A case of meningococcic meningitis starting as diabetic coma was reported by Ward and Driver.[14] Upon recovery from meningitis, the patient was proved to be nondiabetic. Fox, Kuzma, and Washam [15] found a transitory diabetic syndrome in 24.9% of 233 cases and reported 5 in which the blood sugar was 168 to 283 mg. per 100 cc. and the urine contained sugar and acetone. The patients were treated for diabetic acidosis until examination of the spinal fluid proved the existence of meningitis. The authors assumed that involvement of the thalamus, hypothalamus, anterior lobe of the pituitary, and floor of the fourth ventricle disturbed the endocrine regulation of carbohydrate metabolism.

Auditory complications are among the commonest, partial or complete deafness resulting from fibrinous constriction of the auditory nerve or from invasion of the labyrinths with destruction of the end-organs, this being followed by the formation of granulation tissue and bone.[16] Bilateral deafness is likely to lead to loss of speech to an extent directly proportional to the length of time speech has been present. Thus, in children with a small vocabulary mutism develops rapidly.[17]

Less common complications include subdural hematomas,[18] extradural hemorrhage in the thoracic region,[19] gangrene of the toes and causalgia in the ulnar distribution,[18a] and thrombosis of an axillary artery with gangrene of the arm.[19]

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11. Bennett, A. E.: Cerebellar Herniation into Foramen Magnum, J. A. M. A. **100**:1922 (June 17) 1933.

12. Dunphy, E. B.: Ocular Complications of Cerebrospinal Meningitis, Arch. Ophth. **15**:118 (Jan.) 1936. Heath, P.: Visual Sequelae from Epidemic Meningococcus Meningitis, Am. J. Ophth. **20**:401 (April) 1937. Lewis, P. M.: Ocular Complications of Meningococcic Meningitis: Observations in 350 Cases, ibid. **23**:617 (June) 1940.

13. Fox, M. J., and Gilbert, J.: Meningococcic Infections with Articular Complications, Am. J. M. Sc. **208**:63 (July) 1944.

14. Ward, C. W., and Driver, A. A.: Meningococcal Meningitis Starting as Diabetic Coma, Lancet **2**:228 (Aug. 24) 1940.

15. Fox, M. J.; Kuzma, J. F., and Washam, W. T.: Transitory Diabetic Syndrome Associated with Meningococcic Meningitis, Arch. Int. Med. **79**:614 (June) 1947.

16. Hagens, E. W.: Pathology of the Inner Ear in a Case of Deafness from Epidemic Cerebrospinal Meningitis, Ann. Otol. Rhin. & Laryng. **49**:168 (March) 1940.

17. Kinney, C. E.: Loss of Speech Due to Meningitic Deafness, Arch. Otolaryng. **47**:303 (March) 1948.

18. Banks and McCartney.[10] Nelson, J.; Clyne, R. M., and Sharnoff, J. G.: Bilateral Subdural Hematoma—an Unusual Complication of Meningococcus Meningitis, Ann. Int. Med. **25**:862 (Nov.) 1946.

18a. Bernstein, P.: Causalgia and Gangrene: Rare Complications in Meningococcal Meningitis; Report of a Case, New England J. Med. **230**:482 (April 20) 1944.

19. Levin, A., and McElroy, D. M.: A Case of Cerebrospinal Fever with Thrombosis of the Right Axillary Artery, Followed by Gangrene of the Right Arm, Necessitating Amputation, Brit. J. Surg. **31**:240 (Jan.) 1944.

These occurrences are attributed to meningococcic emboli to the vasa vasorum, producing focal necrosis, diapedesis, and a locus for thrombosis.

Complications referable to the nervous system include paralysis of the oculomotor, trochlear, and abducens nerves; facial palsy; hemiplegia; monoplegia; transient blindness; aphasia, and convulsions. Farmer [20] reported that of 300 patients with meningococcic meningitis treated with sulfonamides, 26 had neurologic complications. All occurred within the first 14 days of illness and were distributed as follows: nine had abducens paralysis, with recovery in a few days to 8 months; nine had facial paralysis, eight recovering completely within 12 months; five had auditory-nerve involvement, with no recovery, and three had hemiplegia, two being aphasic and one having homonymous hemianopsia, with all three recovering within four months. The electroencephalogram of one of these patients showed slow waves over the left parieto-occipital area; these disappeared within six months. Less commonly, transverse myelitis or a poliomyelitic type of lesion occurs and carries a prognosis similar to that of the viral disease.[21]

The disease and its complications may be followed by sequelae or residua. Deafness, deaf-mutism, blindness resulting from metastatic endophthalmitis or optic nerve atrophy, strabismus, hydrocephalus, mental enfeeblement, convulsions, hemiplegia, and facial paralysis have been recorded by many.[22] A rather uncommon sequela is slowly developing paraplegia with sensory changes and spinal subarachnoid block, the result of arachnoid adhesions. Laminectomy may be helpful unless the spinal cord is severely damaged.[23] Apparently, these adhesions can occur whether or not intrathecal therapy is used. Bailey [24] showed that sulfonamides and penicillin do not restrain the proliferation of fibroblasts, in their attempt to organize the exudate; he, therefore, advised a guarded prognosis after meningitis.

Ballard and Miller,[25] in a study of 60 men seen in a Royal Air Force center who had had meningitis three to six months previously, found 53 who complained of such symptoms as insomnia, dizziness, difficulty in concentrating, muscular pains, and backache. There was a striking relation to the degree of neurotic predisposition. The authors believed that this symptom complex should be regarded as a psychosomatic reaction. On the other hand, Pai [26] described personality defects, intel-

20. Farmer, T. W.: Neurologic Complications During Meningococcic Meningitis Treated with Sulfonamide Drugs, Arch. Int. Med. **76**:201 (Oct.) 1945.

21. Turner, J. W. A.: Spinal-Cord Lesions in Cerebrospinal Fever, Lancet **1**:398 (March 13) 1948.

22. McLean, S., and Caffey, J. P.: Sporadic Meningococcus Meningitis: Sequelae Following Specific Serum Therapy in Infancy and Early Childhood, J. A. M. A. **87**:91 (July 10) 1926. Borovsky, M. P.: A Clinical Study of Meningococcic Meningitis: An Analysis of 190 Cases Observed in a Period of 18 Months, Am. J. M. Sc. **179**:82, 1930. Hodes, H. L., and Strong, P. S.: Treatment of Meningococcic Meningitis with Sulfonamides, J. A. M. A. **119**:691 (June 27) 1942. Dingle, J. H., and Finland, M.: Diagnosis, Treatment and Prevention of Meningococcic Meningitis, with Résumé of Practical Aspects of Treatment of Other Acute Bacterial Meningitides, War Med. **2**:1 (Jan.) 1942. Hoyne and Brown.[5]

23. Turner.[21] Stewart, H. H.: A Case of Paraplegia After Cerebrospinal Meningitis, Brit. M. J. **2**:319 (Sept. 8) 1945.

24. Bailey, P.: Chronic Leptomeningeal Thickening Following Treatment of Meningitis with Sulfa Drugs, Ann. Surg. **122**:917 (Dec.) 1945.

25. Ballard, S. L., and Miller, H. G.: Sequelae of Cerebrospinal Meningitis: An Analysis of 60 Cases, Lancet **2**:273 (Sept. 1) 1945.

26. Pai, M. N.: Personality Defects and Psychiatric Symptoms After Cerebrospinal Fever in Childhood: Meningococcal Encephalopathy, J. Ment. Sc. **92**:389 (April) 1946.

lectual deterioration, conduct disorders, restriction of interest, instability, and vulnerability to stress as sequelae. He postulated a meningococcic encephalopathy as their basis.

Slesinger [27] reported sequelae, such as hydrocephalus, deafness, speech defect, and mental retardation, in 35.6% of 42 children treated with antimeningococcic serum whom he examined 6 months to 4½ years later. Hauge [28] cited Aaser as showing that 58% of patients recovering from meningococcic meningitis before the advent of serum therapy had residual defects; this was reduced to 25.3% after the use of serum became widespread. Hauge reexamined 66 patients six months to eight years after they had had sulfonamide therapy for the disease and found that 9% had permanent organic defects and 35% had combined organic and neurasthenic residua, such as dizziness, headaches, poor memory, fatigability, insomnia, and restlessness.

One would surmise that the incidence of residua would be less with the use of chemotherapeutic and antibiotic agents than with serum. In order to determine whether this was true, the present study was undertaken.

TABLE 2.—*Mortality Percentages for Meningococcic Meningitis at Indianapolis General Hospital Jan. 1, 1930, to Dec. 31, 1948*

Therapy	No.	No. Recovered	No. Died	Mortality
Serum	288	117	171	59.3%
Sulfonamides	105	88	17	16.2%
Sulfonamide-Penicillin	55	44	11	20.0%
Penicillin	5	3	2	.....
Over-all Total	453	252	201	44.3%

PRESENT INVESTIGATION

The record of every patient with proved meningococcic meningitis who was admitted to the Indianapolis General Hospital between Jan. 1, 1930, and Dec. 31, 1948, was examined and placed in one of three treatment groups: (*a*) patients receiving an accepted commercial antimeningococcic serum; (*b*) patients to whom sulfonamides were administered in standard, routine doses (a few had one or two injections of penicillin intrathecally as well), and (*c*) patients who received routine doses of sulfonamides plus around-the-clock injections of penicillin. Most of these also had one to nine intrathecal injections of 10,000 to 15,000 units of penicillin. Only five patients received penicillin alone, and hence are not included in this study. The serum was generally administered intramuscularly, supplemented by frequent intrathecal injections. The sulfonamides employed were sulfanilamide, sulfamerazine, sulfadiazine, and, in a few instances, sulfathiazole. However, for the purposes of this study they were considered as a single drug family, the most popular member of which was sulfadiazine. In all cases the drug was given by mouth; in many it was injected intravenously once or twice shortly after admission, and on rare occasions it was injected intrathecally or subcutaneously.

Table 2 presents the total number of admissions and therapeutic results for 453 patients admitted to the Indianapolis General Hospital during the 19-year period under consideration.

It was possible to trace and to examine personally 51 of the 252 recovered patients. In addition, electroencephalographic studies were carried out on 34 patients, and psychometric evaluations on 35.

27. Slesinger, H. A.: Complications and Sequelae of Meningococcic Meningitis During Infancy and Early Childhood, Pennsylvania M. J. **36**:327 (Feb.) 1933.

28. Hauge, M. F.: Defects Following Purulent Meningitis Treated with Sulfonamides, Nord. med. **37**:469 (March 5) 1948.

Of the 35 patients given psychometric examinations, 5 were children. Four of these were given the Binet test and scored intelligence quotients of 92, 92, 82, and 73. The fifth was given the Merrill-Palmer test and scored an intelligence quotient of 101. For the 30 adults, the Wechsler-Bellevue General Intelligence Scale,[29] the Kohs Block test, and the Memory-for-Designs test [30] were used.

The Wechsler-Bellevue General Intelligence Scale consists of a battery of 10 subtests, which yield full, verbal, and performance intelligence quotients. There were three ratings of from 70 to 80, five of from 80 to 90, seven of from 90 to 100, five of from 100 to 110, five of from 110 to 120, one of from 120 to 130, and four of from 130 to 140.

TABLE 3.—*Data on Serum Therapy Group*

Name	Age at Time of Illness	Present Age	Sex	Race	Coma	Day Cells Were Below 50	Day Temperature, Normal	Therapy*	Complications	Residua	EEG*	Psychometric Defects*
E. G.	12	32	F	N	+	14	22	IT, IM	Transient internal strabismus	None	—	—
N. O.	9	29	M	W	+	18	22	IT, IM	None recorded	Right hemiparesis, hypoplasia, Jacksonian attacks	Amplitude asymmetry from left hemisphere	None
B. J. H.	6	26	F	W	+	29	30	IT, IV, IM	Right hemiplegia, 24th day	Right hemiplegia; hypoplasia; Babinski sign	—	—
R. H.	11	31	M	W	+	16	15	IT, IV	None	None	Normal	—
B. H.	4	24	F	W	+	16	25	IT, IV, IM	Transient external strabismus	None	—	—
J. C.	4	24	M	W	+	10	20	IT, IV, IM	Panophthalmitis (O. D.) 9th day	Blind, right eye	—	—
L. B.	3	23	F	N	+	23	38	IT, IM	Transient left facial paralysis	Deaf, left ear	Normal	++
W. A.	16	26	M	W	0	7	13	IT, IM	Deaf left ear, 3d day; transient partial left oculomotor paralysis	Deaf, left ear	Normal	None
E. S.	3	15	M	W	0	18	16	IT, IV, IM	None	None	Normal	None
D. C.	16	30	M	N	+	7	10	IT, IV	None	None	Normal	None
J. S.	27	43	M	W	0	13	3	IT, IM	None	None	Normal	+
W. O.	7	22	M	W	+	19	20	IT, IM	Deaf bilaterally	Deaf bilaterally	Normal	+
J. A.	38	49	M	W	+	15	11	IT, IM	None	None	—	—
R. D.	24	35	M	N	0	42	7	IT, IM	None	Adhesive spinal arachnoiditis	—	—
A. A.	2	22	M	N	+	No record	18	IT, IM	None	Monoparesis (left leg)	Normal	None
O. D.	13	33	M	N	+	10	9	IT, IM	None	None	Normal	++
L. T.	18	38	M	N	0	30	26	IT, IM	Fibrinous pericarditis	None	—	—

* The minus sign (—) indicates the examination was not made.

The Kohs Block test is a visual-motor test involving the analysis or reproduction of geometric designs. The original 17-design test was used. The Memory-for-Designs test is a visual-motor test consisting of 15 simple designs to be reproduced after a presentation of five seconds. It is useful in any battery in which brain damage is suspected.

The test results were tabulated and indications of brain damage graded as mild, moderate, or severe. Mild damage (+) was evidenced by either a low rating on the Memory-for-Designs

29. Wechsler, D.: The Measurement of Adult Intelligence, Ed. 3, Baltimore, Williams & Wilkins Company, 1944.

30. Graham, F., and Kendall, B.: Performance of Brain-Damaged Cases on a Memory-for-Designs Test, J. Abnorm. & Soc. Psychol. **41**:303 (July) 1946.

TABLE 4.—*Data on Sulfonamide-Treated Group*

Name	Age at Time of Illness	Present Age	Sex	Race	Coma	Day Cells Were Below 50	Day Temperature Was Normal	Therapy	Complications	Residua	EEG*	Psychometric Defects*
J. S.	4	17	M	W	+	13	15	Sulfanilamide; 10,000 U. antitoxin	Deaf right ear; weak left leg	Deafness on right	Normal	None
P. T.	36	40	M	N	+	Adm. LP only†	4	Sulfadiazine; 10,000 U. pen. IT once‡	None	None	Normal	+++
G. F.	39	47	M	W	+	5	11	Sulfadiazine	Left hemiplegia 2d day	Mild left hemiparesis	Normal	None
L. B.	8	15	M	W	0	3	6	Sulfanilamide	None	None	F_3 throughout, symmetric	None
D. B.	7	13	F	W	0	7	8	Sulfanilamide	None	None	Normal	None
W. C.	3	9	M	N	0	Adm. LP only†	7	Sulfanilamide	Synovitis, right ankle	Deafness on left	Normal	None
P. P.	17	23	M	W	+	21	5	Sulfadiazine; 15,000 U. pen. IT once‡	Transient diplopia	None	Normal	None
L. P.	3	9	M	N	0	12	12	Sulfanilamide; 10,000 U. pen. IT once‡	None	None	—	—
R. P.	15	20	M	N	+	8	5	Sulfamerazine	Optic neuritis, O. D.	Primary optic atrophy, O. D.; right hemiparesis	Normal	++
H. M.	53	60	M	W	+	10	11	Sulfadiazine	Transient right facial palsy	None	Normal	None
A. L.	40	46	F	W	+	Adm. LP only†	3	Sulfadiazine	None	None	—	—
M. R.	10	23	M	W	0	10	6	Sulfanilamide	None	None	Normal	—
G. B.	7	17	F	W	0	5	25	Sulfanilamide; serum IT once§	Panophthalmitis (O. D.) 2d day	Blind O. D.	Normal	+
L. C.	21	31	F	W	+	6	10	Sulfanilamide	None	None	Normal	None
D. P.	14	17	M	N	+	6	17	Sulfadiazine; 15,000 U. pen. IT twice‖	Synovitis right knee	None	—	—
S. R.	4	9	F	W	+	No record	8	Sulfanilamide	None	None	Normal	None
C. Y.	4	10	M	N	+	No record	7	Sulfanilamide	Deafness 1st day	Deaf bilaterally; mutism	—	—
R. H.	3	9	F	W	0	6	7	Sulfanilamide; 10,000 U. pen. IT once‡	None	None	Normal	None
D. W.	68	73	F	W	+	No record	4	Sulfadiazine	None	None	—	—
S. B.	16	23	M	W	+	8	14	Sulfadiazine 20,000 U. serum IV#	None	None	S_2, left hemisphere	None
D. W.	8	15	F	W	+	8	2	Sulfadiazine	None	None	—	++
D. J.	16	22	M	N	+	7	6	Sulfamerazine	None	None	Normal	None
W. W.	3	10	M	W	0	5	3	Sulfadiazine	Deafness on right	Deaf on right	Normal	None

* The minus sign indicates the examination was not made.
† Lumbar puncture made only on admission.
‡ Intrathecal injection of 10,000 U. penicillin made once.
§ Intrathecal injection of serum once.
‖ Intrathecal injection of 15,000 U. penicillin once.
Intravenous injection of 20,000 U. serum.

test or a high one on the Kohs Block test, or it was given when the Wechsler-Bellevue test showed some signs of deterioration. A rating of moderate damage (++) was given when low scores were made on two of the tests or when the Memory-for-Designs score was extremely high. A grading of severe damage (+++) was given when all the scores were low or when the Memory-for-Designs rating was higher than 10.

Each patient's record during his illness with meningitis was reviewed, and attempts were made to correlate the acute phase with present residua. Table 3 presents data for the patients treated with serum; Table 4, data for the group treated with sulfonamides, and Table 5, data for the group treated with sulfonamides and penicillin.

TABLE 5.—*Data on Sulfonamide-Penicillin-Treated Group*

Name	Age at Time of Illness	Present Age	Sex	Race	Coma	Days Cells Below 50	Days Temperature Normal	Therapy	Complications	Residua	EEG*	Psychometric Defects*
M. M.	34	37	F	W	+	8	12	Sulfadiazine; pen. 30,000 U. q. 3 h.	None	None	Normal	None
L. T.	42	46	M	N	0	Adm. LP only	5	Sulfadiazine; pen. 40,000 U. IT once, then q. 3 h.	None	None	Normal	+++
D. R.	45	48	F	W	+	9	2	Sulfadiazine; pen. 10,000 U. IT once, then q. 3 h.	None	None	Normal	None
S. M.	2	4	F	W	0	Adm. LP only	2	Sulfadiazine; pen. 10,000 U. IT once, then q. 3 h.	None	None	Normal	None
M. F.	17	22	F	W	+	13	16	Sulfadiazine; pen. 15,000 U. IT twice, then q. 3 h.	Synovitis right knee, 7th day	None	—	—
J. D.	19	24	M	W	+	6	7	Sulfadiazine; pen. 15,000 U. q. 3 h.	None	None	—	None
J. T.	12	16	F	W	0	4	5	Sulfadiazine; pen. 15,000 U. IT once, then q. 3 h.	None	None	Normal	+++
J. H.	35	37	M	W	+	11	4	Sulfadiazine; pen. 50,000 U. q. 3 h.	None	None	Normal	None
N. H.	16	21	F	W	+	5	4	Sulfadiazine; pen. 15,000 U. IT 3 times, then q. 3 h.	None	None	Normal	++
W. P.	34	38	M	W	+	21	26	Sulfadiazine; pen. 15,000 U. IT 9 times; IM; transfusions	Critical several days; toxic	None	—	+++
T. C.	25	29	F	W	0	6	7	Sulfanilamide; pen. 15,000 U. IT once, then q. 3 h.	Transient papilledema O. D.	None	—	—

Thus, of the 17 serum-treated patients, 10 had residual defects. The distribution of these defects was as follows: hemiparesis, two, one of whom showed electroencephalographic asymmetry; monoparesis, one; adhesive spinal arachnoiditis, one; unilateral blindness, one; deafness, three, two of whom showed, in addition, evidence of organic damage to the brain, and brain damage, without other indications of impairment, two.

The patient with spinal arachnoidal adhesions was a Negro, R. D., who had meningitis in 1934, at the age of 21. He received serum intrathecally, intravenously, and intramuscularly in the routine fashion and recovered without apparent ill-effects. Fourteen years later he noted painless, progressive weakness, clawing, and atrophy of his right hand and complained that he no longer was able to lift 200 lb. (90.7 kg.) bags with it. His legs had become clumsy and stiff.

Examination disclosed atrophy of the right supraspinatus, infraspinatus, latissimus dorsi and triceps muscles; the lower part of the forearm and the hand on the right, and the thigh and leg on the left. Moderate weakness accompanied the atrophy. Tendon reflexes in the right arm and left leg were reduced; there was no Babinski or confirmatory sign. Hypalgesia was present over the ulnar aspect of the right forearm and hand.

Roentgenograms of the spine revealed nothing abnormal. The Kline and Kahn reactions of the blood, and the Wassermann reaction of the spinal fluid were negative. The spinal fluid protein was 130 mg. per 100 cc. on one occasion and 185 mg. per 100 cc. on a second.

Spinal subarachnoid block was demonstrated on lumbar puncture. In myelograms with ethyl iodophenylundecylate (pantopaque*), the dye was seen to break up into many globules and pockets and to ascend no higher than the seventh thoracic segment.

In the sulfonamide-treated group, 11 of the 23 patients had defects, with the following distribution: hemiparesis, two; deafness, three; deaf-mutism, one; unilateral blindness, one; primary optic atrophy, one; electroencephalographic abnormalities, two, and signs of organic brain damage, four. One patient, R. P., had three defects: mild right hemiparesis, primary optic atrophy on the right, and psychometric indications of brain injury.

The only detectable defects among the 11 patients in the sulfonamide-penicillin-treated group lay in the psychometric sphere and consisted of brain damage in four instances.

Reference to Tables 3, 4, and 5 reveals that while all patients had physical and neurologic examinations, several failed to have electroencephalographic or psychometric studies. Therefore, for a fair comparison of the findings in each group, only those patients who had all three methods of examination were included in a statistical analysis, a method which makes allowances for small samples being used. This analysis sought to compare data in the three groups with respect to the following factors: (1) mean number of defects per patient; (2) percentage of patients having defects; (3) percentage of complications occurring during the acute phase of the illness; (4) comparative incidence of psychometric defects; (5) comparative incidence of physical defects; (6) relation of coma to incidence of residua.

Of the nine completely studied serum-treated patients, seven, or 78%, had a total of 10 different defects. Five were apparent on physical examination; one, on electroencephalographic study, and four, in psychometric studies. Of the 16 completely studied sulfonamide-treated patients, 9, or 56%, exhibited a total of 12 defects. Seven were observed clinically; two, electroencephalographically, and 3, psychometrically. Of the seven similarly studied patients in the sulfonamide-penicillin series, three, or 43%, were found to have one defect each, all being established by psychometric evaluation.

The mean number of defects per patient in the serum-treated group was 1.1 (standard deviation, 0.782); in the sulfonamide-treated group, 0.8 (standard deviation, 0.857), and in the sulfonamide-penicillin-treated series, 0.4 (standard deviation, 0.536). The difference between the means of the serum group and that of the sulfonamide group was 0.3, which, being less than twice the standard error of the difference (0.336), is not statistically significant. Similarly, the difference between the mean number of defects for the sulfonamide group and that for the sulfonamide-penicillin group (0.4) did not differ by as much as twice the value of the standard error of the difference (0.294) and thus carries no statistical significance. The difference between the mean for the serum group and that for the

sulfonamide-penicillin group (0.7) was barely twice the standard error of the difference (0.33) and therefore probably is not statistically significant.

Thus, no statistically significant difference in the mean number of defects per patient is revealed by this comparison of the three differently treated groups.

A comparison of the number of completely studied patients who had defects in the three series revealed residua in 78% of the serum-treated group, in 56% of the sulfonamide-treated group, and in 43% of the sulfonamide-penicillin-treated group. The difference between the number for the serum-treated and that for the sulfonamide-treated groups was 22%. The standard error of the difference between the percentages is computed to be 18.6%, indicating that the difference is not statistically significant; nor is the 13% difference for the sulfonamide-treated and the sulfonamide-penicillin-treated groups, since the standard error of the difference between the two percentages is 22.5%. Although there were 35% more patients with defects in the serum-treated group than in the sulfonamide-penicillin-treated series, the standard error of the difference is computed to be 23.5%. Since the difference of 35% is less than twice the standard error of the difference, it cannot be considered statistically significant.

With respect to the number of complications occurring during the acute phase of the illness, for the determination of which information was obtained from the hospital charts only, it was found that 47% of the patients in the serum-treated group, 43% of the patients in the sulfonamide-treated group, and 27% of the patients in the sulfonamide-penicillin-treated series had complications. There is a difference of 20% between the number of the serum-treated group and that of the sulfonamide-penicillin treated group. However, this is less than twice the calculated standard error of the difference (18%) and therefore is not statistically significant. The same conclusion may be reached regarding the differences between the serum and the sulfonamide series and between the sulfonamide and the sulfonamide-penicillin groups (16%).

Comparison of the number of defects found on psychometric examination shows that 44% of the serum-treated group, 19% of the sulfonamide-treated group, and 43% of the sulfonamide-penicillin-treated group had such defects. The difference between the serum and the sulfonamide-penicillin group is obviously not significant. The 25% difference between the serum and the sulfonamide groups and the 24% difference between the sulfonamide and the sulfonamide-penicillin series are less than twice the standard error of the difference (19%); hence, neither difference is statistically significant.

Although no defects on physical examination alone were evident in the small sulfonamide-penicillin group, it was necessary that a numerical defect (1) be assumed in order to utilize the statistical formula. When the three series are then compared with respect to these observations, it is found that physical defects were 55% commoner in the serum-treated group and 38% commoner in the sulfonamide-treated group than in the sulfonamide-penicillin-treated series. These differences are more than three times the calculated standard errors of the differences (17 and 12%, respectively) and are therefore statistically significant. The 17% difference between the serum and the sulfonamide group is less than twice the standard error of the difference (21%), and hence not statistically significant.

Table 6 is a correlation of the presence or absence of residual defects with the state of consciousness on admission, the duration of cerebrospinal pleocytosis, and

the duration of fever. A cell count of 50 per cubic millimeter was chosen arbitrarily, since a survey of all the meningitis records revealed that clinical improvement paralleled the drop in the cell count, and after this reached 50 too few punctures were performed to permit the establishment of an exact time of return to normal figures.

Table 6 indicates that of the patients admitted in coma, 55% had residua, and of those not comatose 67% had defects. This difference of 12% is not statistically significant. There is no significant correlation between the incidence of residua and the pleocytosis in any of the groups. The return of temperature to normal levels, similarly, seems to bear no distinct relation to the incidence of residua. It is noted that in the serum-treated group the temperature returned to normal in 17 days in patients exhibiting residua, whereas in patients having no residua it returned to normal in 13 days. This is probably because serum is not as efficacious in combating complications and their attending febrile reactions as are chemotherapeutic and antibiotic agents.

TABLE 6.—*Correlation of State of Consciousness, Pleocytosis, Duration of Fever, and Residua in 32 Completely Studied Cases*

	No. Serum-Treated Patients	No. Sulfonamide-Treated	No. Sulfonamide-Penicillin-Treated	Total No. Patients	
				No.	%
Comatose on admission					
With residua	5	5	1	11	55
Without residua	1	5	3	9	45
Noncomatose					
With residua	2	4	2	8	67
Without residua	2	2	1	4	33
Average day on which CSF cells was below 50/cu. mm.					
With residua	15	7	5		
Without residua	13	9	9		
Average day temperature reached normal					
With residua	17	10	5		
Without residua	13	8	5		

COMMENT

During the 19 years covered by this analysis, the mortality rates with serum therapy, sulfonamide therapy, and combined penicillin-sulfonamide treatment were 59.3%, 16.2%, and 20.0%, respectively. These figures are in accord with the reports of others.

This study compares and evaluates the effectiveness of these three methods of therapy upon the incidence of residua. Of the 51 unselected patients who were given physical and neurologic examinations, 32 had, in addition, electroencephalographic and psychometric studies. By the application of statistical methods which make allowances for small samples, certain relationships are revealed. Nineteen, or 59%, of the 32 patients were shown to have residua, such as hemiparesis, monoparesis, deafness, blindness, optic atrophy, arachnoid adhesions, cerebral dysrhythmia, and psychometric indications of brain damage. Of the serum-treated patients, seven (78%) had a total of 10 different defects; of the sulfonamide-treated group, nine (56%) had a total of 12 defects, and of the sulfonamide-penicillin series, three (43%) had 1 defect each. While these differences appear to be gross ones, on analysis they are shown to have no statistical significance. It seems, therefore, that

the mean number of defects per patient and the percentage of patients with defects are practically the same with all three methods of therapy. One puzzling feature, however, is that defects apparent on physical examination are three times as common in patients treated with serum or with sulfonamides as in those treated with combined penicillin and sulfonamide. This is difficult to explain, inasmuch as corollaries referable to coma, pleocytosis, and duration of fever are not supportive. The only apparent explanation is that the complications occurring during combined therapy were transient, whereas those occurring during serum or sulfonamide therapy were often of a permanently disabling nature, such as panophthalmitis, deafness, and cerebral vascular thrombosis. It would seem that the addition of penicillin tends to lessen this type of complication.

The discrepancy between Slesinger's finding of 35.6% residua in serum-treated patients and the 78% found in this study, and Hauge's report of permanent defects in 9% of a sulfonamide-treated series, as against 56% in this study, is probably due to the advantage of having electroencephalography and a psychometric battery, which detected masked residua.

Twenty-one of the 51 patients (41%) had complications, most of which occurred within the first two weeks if illness. Eight (47%) were in the serum group; 10 (43%), in the sulfonamide group, and 3 (27%), in the sulfonamide-penicillin series. When subjected to analysis, these differences are not statistically significant. Thus, it appears that while the incidence of complications is not affected by the type of therapy employed, their character and severity may be influenced by the addition of penicillin.

Ten (31%) of the 32 completely studied patients exhibited psychometric evidence of brain damage. There was no statistically significant difference in incidence among the three groups. This rather frequent occurrence of brain damage lends support to Pai's opinion that the personality and psychiatric defects are the result of meningococcic encephalopathy. These findings also support his contention that chemotherapy does not prevent the development of such residua.

Although the mortality rate is higher in comatose than in noncomatose patients, the incidence of residua seems not to be significantly different regardless of the type of treatment employed.

SUMMARY

In order to compare the incidence of residual defects following serum therapy, sulfonamide therapy, and combined sulfonamide-penicillin therapy in patients with meningococcic meningitis, 51 unselected persons who had recovered from this disease 1½ to 20 years previously were given physical and neurologic examinations. Thirty-two received electroencephalographic and psychometric studies as well.

The results in each of the three differently treated groups were analyzed statistically with respect to the mean number of defects per patient, the percentage of patients having defects, the incidence of psychometric and physical defects, the incidence of complications, and the relation of coma to the incidence of defects.

It was found that, although sulfonamide and sulfonamide-penicillin therapy have greatly reduced the mortality rate as compared with that for serum therapy, the incidence of complications and the number and percentage of defects in the form of physical, neurologic, electroencephalographic, or psychometric residua showed no statistically significant differences for the three methods. It was observed, how-

ever, that physical defects were three times as common in patients treated with serum or with sulfonamides as in those who received combined sulfonamide-penicillin therapy. In the last group defects were discovered only on psychometric evaluation. Presumably, the addition of penicillin lessens the incidence of severe complications, which lead to physical residua.

The presence or absence of coma bore no relation to the incidence of residua.

CONCLUSIONS

1. Although the use of sulfonamide or of combined sulfonamide-penicillin therapy in cases of meningococcic meningitis has greatly reduced the mortality rate in this disease as compared with that when serum therapy was employed, there are no statistically significant differences in these three methods of therapy with respect to the incidence of complications or the number and percentage of residual defects that ensue.

2. Defects apparent on physical examination, in contradistinction to those discovered psychometrically, are significantly less frequent when a combination of sulfonamide and penicillin is employed than when either sulfonamide or serum is used alone. Presumably, the addition of penicillin reduces the likelihood of damaging complications.

3. A battery of psychometric tests may unmask evidences of organic brain damage not apparent on physical or electroencephalographic examination.

Hazel H. Stevens, Ph.D., made the psychometric studies, and Philip F. D. Seitz, M.D., the statistical analyses in this report.

ABSTRACT OF DISCUSSION

Dr. Ellsworth C. Alvord Jr., Washington, D. C.: Dr. Ross's paper is particularly timely because in the next one, two, or three years we are due to have another epidemic of meningococcic meningitis. Now is a good time to review some of the concepts of how to treat this disorder.

However, I should like to comment on Dr. Ross's results. One must be careful not to interpret his precise statement ("There is no statistically significant difference" in the various groups) as saying that "there is no difference" in these groups.

He has kindly lent me his paper, and as I have reviewed the figures, it has become obvious that, with one exception, there is a definite trend, with the serum-treated patients having the highest incidence and the sulfonamide-penicillin-treated patients the lowest incidence of residua.

It has further become evident that the ages of the various groups differ in his series, the serum-treated patients being younger (average, 11 years) than either the sulfonamide-treated series (average, 15 years) or the penicillin-sulfonamide-treated series (average, 22 years). Perhaps this age differential favored the trend he found, for it is well known that the mortality rate is greatest in infants.

Dr. Ross was unable to follow some 80% of the patients who were treated. It would seem to me that it is in this group which is very difficult to follow that one must look for the larger number of the complications which might prevent the patient from responding to follow-up inquiries.

Another difficulty, from the clinical point of view, is the determination of the precise etiologic factor in cases of chronic adhesive arachnoiditis or epilepsy which comes on many years after the attack of meningitis.

Although the pathology of meningococcic meningitis is fairly well known, with encephalitis, vascular occlusion, necrosis of brain tissue, and fibrosis of the leptomeninges the

most prominent features (Alexander, W. S.: Influence of Chemotherapy in the Pathology of Purulent Leptomeningitis, ARCH. NEUROL. & PSYCHIAT. **63**:73 [July] 1949), the pathogenesis of these lesions remain in considerable doubt.

Meningococcic meningitis is far from being a simple disease. Many variable factors are to be considered in therapy, in addition to the type of treatment: the age of the patient, the severity and duration of the disease, the type and strain of the Meningococcus, and the rather vague, but nonetheless real, factor of individual susceptibility (Aycock, W. L., and Mueller, J. H.: *Bact. Rev.* **14**:115, 1950. Black-Schaffer, B.; Hiebert, T. G., and Kerby, G. P.: Experimental Study of Purpuric Meningococcemia in Relation to Shwartzman Phenomenon, *Arch. Path.* **43**:28 [Jan.] 1947).

Of all the factors, the most intriguing to me is the toxemia. In 1907 Flexner, and in 1935 Branham and her co-workers (Branham, S. E.; Lillie, R. D., and Pabst, A. M.: *Bact. Rev.* **4**:59, 1940; *Pub. Health Rep.* **52**:1135, 1937) demonstrated that the toxins of the Meningococcus were just as effective as the living organism producing the purulent meningitis, and Branham has emphasized that serum and sulfonamides act synergistically, being much more effective when in combination than when either is acting alone; indeed, some strains are quite resistant to either serum or sulfonamide given alone (Branham, S. E.: *Pub. Health Rep.* **55**:12, 1940).

The recent work by Miller and Kun and their co-workers (Miller, C. P.; Hawk, W. D., and Boor, A. K.: *Science* **107**:118, 1948. Kun, E., and Miller, C. P.: *Proc. Soc. Exper. Biol. & Med.* **67**:221, 1948. Kun, E., and Abood, L. G.: ibid. **71**:362, 1949) has shown that meningococcic toxin inhibits or poisons certain enzymes in the carbohydrate metabolism, namely, succinic dehydrogenase and pyruvic oxidase. They also have noted that penicillin has an antitoxic, protective value in mice. This rather fundamental research would seem to offer a fruitful field for advance in the treatment of meningococcic meningitis.

DR. ROLAND P. MACKAY, Chicago: Dr. Ross's paper is instructive, optimistic, and suggests that the mortality from meningococcic meningitis has been greatly diminished, but that the complication among those who live is as high as ever.

This paper bears upon a point which is considerably debated nowadays, namely, the advisability of the intrathecal injection of penicillin. It has been insisted by many workers that many of the complications of meningitis are due to the use of the therapeutic agents. One of the oldest traps into which the medical investigator can fall is to attribute the results of a disease to the treatment used for the disease, rather than to the disease itself.

It would appear, from the slides which Dr. Alvord has shown, that it is the disease which produces the complication, and not the treatment, intrathecal or other.

I should like to ask Dr. Ross whether he has had the opportunity to divide his cases in such a way as to show whether complications are more frequent among patients receiving penicillin intrathecally than among those receiving it parenterally or intramuscularly.

DR. ALEXANDER J. ROSS, Indianapolis: No doubt, if I had been able to find more patients who had had the disease and recovered, there would have been alterations in the statistics, but I rather think the statistics do demonstrate a trend which would be maintained.

I did not divide the patients who had had penicillin intrathecally from those who had not; in fact, practically all of them, during this period, received intrathecal injections of penicillin routinely.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

THE DEPLANTATION OF FRAGMENTS OF NERVOUS SYSTEM IN AMPHIBIANS: I. CENTRAL REORGANIZATION AND THE FORMATION OF NERVES. PAUL WEISS, J. Exper. Zool. **113**:397 (March) 1950.

The technique for isolating fragments of central nervous system in a trophically favorable, but otherwise indifferent, site (the dorsal fin of urodele larvae) is called deplantation. The isolated neural tissue was later provided with an effector organ (limb, heart, etc.), and the resumption of nerve connections and functional activity was followed.

All results pertaining to nerve outgrowth, nerve orientation, fasciculation, and terminal connection are considered in this paper, while those dealing with functional activity will be reported in a subsequent article.

Fragments of spinal cord or brain of larval or adult urodeles were deplanted, either without additional injury or after laceration, into the dorsal fin of other larvae, where they became vascularized and incorporated. They exhibited varying degrees of disorganization and degeneration, as well as proliferation and reconstruction. Nerve fibers which regenerated from the residual portions, if allowed, would innervate musculature and cause functional activity of the deplants.

The formation of strong connecting nerves between neural deplants and grafted limbs occurred irrespective of the relative positions of source and recipient and involved two separable principles —orientation and fasciculation.

If the limb had been forced into alignment to form a straight pathway from the nerve source along the fibrous matrix of the connective tissue of the fin, then the pioneer fibers were guided straight to their destination. Otherwise the nerve course was circuitous. These facts confirm "contact guidance" and rule out "chemotropic" and "galvanotropic" concepts.

Nerves form by accretion around pioneering fibers which have succeeded in making terminal connections. This process is called "fasciculation," and it implies that a pioneering fiber, in consequence of acquiring peripheral connections, becomes so changed that it can serve as a preferential traffic line for new nerve sprouts. The actual mechanism for "fasciculation" is still obscure.

Although they came from sources devoid of primary motor or sensory neurones, the outgrowing sprouts of cord or hindbrain formed peripheral connections with skin and muscle. Thus, central neurones can provide functionally effective peripheral innervation. Unlike regular peripheral nerve fibers, they showed no selectivity in their terminal relations.

While brain parts anterior to the medulla oblongata (midbrain, thalamus, forebrain) produced nerve connections with the limb grafts, motile function was lacking, and secondary atrophies resulted.

In addition to the above results, the following unrelated observations are reported. 1. Hearts deplanted to the fin continued to beat permanently, and deplanted fragments of gut continued to move peristaltically, thus making excellent objects for chronic physiological and pharmacological studies under direct visual control. 2. The nonspecificity of the sustaining influence of the nervous system on regeneration was proved by the fact that limbs innervated by intracentral nerve fibers were capable of regeneration. 3. Cells of the deplanted thalamus produced melanin, whereas deplanted infundibulum caused permanent expansion of the host chromatophores near the graft site. These effects may be distinguished from the over-all darkening effect of pituitary deplants. 4. Only deplants of nervous system could stimulate growth in the surrounding fin tissue.

REID, New Brunswick, N. J.

THE STRUCTURE OF THE AXON FILAMENTS OF THE GIANT NERVE FIBERS OF LOLIGO AND MYXICOLA. F. O. SCHMITT, J. Exper. Zool. **113**:499 (April) 1950.

The fibrous constituents of formalin-fixed and of unfixed axoplasm of the giant fibers of the squid, Loligo pealii, and of the marine annelid Myxicola infundibulum were dispersed by treatment in a minute volume of distilled water. This material, which was transferred to grids, dried, and often shadowed with a thin layer of chromium, was studied under the electron microscope.

In fixed axons there were nodose, frequently contorted, filaments of indefinite length and having widths of between 75 and 200 A. Occasionally axial discontinuities occurred, which were fairly regularly spaced along the filaments. Since these filaments differ in width and structure from the dense-edged fibrils previously called "neurotubules," Schmitt concludes that the latter are derivatives of the connective tissue sheath which may contaminate isolated axon preparations.

In unfixed material, filaments about 100 to 150 A. in width, with relatively smooth edges, were observed. When aqueous dispersions of unfixed axoplasm are formalinized, the filaments resemble those obtained from fixed axons.

Schmitt discusses the bearing of these observations on the structure of the normal axon and the problem of neurofibrils.

REID, New Brunswick, N. J.

FURTHER EXPERIMENTS ON BLOCKING PITUITARY ACTIVATION IN THE RABBIT AND THE RAT. C. H. SAWYER, J. E. MARKEE, and J. W. EVERETT, J. Exper. Zool. **113**:659 (April) 1950.

Sawyer, Markee, and Everett have studied the effects of blocking agents of adrenergic, cholinergic, ganglionic, and central synapses on the neurohumoral control of luteinizing-hormone release from the adenohypophysis of rabbits (105 females) and rats (35 females).

With the chloroethylamine derivatives, SKF-501, dibenamine,® and 2-dibenzylaminoethanol, a positive correlation was found in the rabbit between ability to block the coital stimulus from reaching the hypophysis and capacity to protect against twice-lethal doses of epinephrine. A negative correlation was observed between the central excitatory activity of these agents and their potency in blocking pituitary activation. The pituitary-activation mechanism in the rat reacted to these drugs in a manner almost identical to the response in the rabbit. These results confirm the hypothesis that these agents prevent pituitary activation by adrenergic blockade.

The imidazoline derivatives, benzazoline and C-7337, failed to block pituitary activation in either species, although C-7337 can develop rapid protection against epinephrine toxicity. Since the failure cannot be attributed to inability of these agents to reach the effector cells, it would appear that imidazoline derivatives fail because they lack the particular chloroethylamine property which blocks the natural adrenergic mediator (not necessarily epinephrine).

Atropine, the anticholinergic drug, was successful in blocking pituitary activation in both species. Pentobarbital, the central anesthetic, was effective in the rat, where it could be injected prior to the normal time of the neurogenic stimulus, but was not effective in the rabbit, although injection by vein was made 12 seconds after coitus. Hence, it is assumed that the failure in the rabbit was due to temporal considerations. The ganglion-blocking agent, tetraethylammonium, failed in both species. These collective data suggest that the site of atropine block is located between the hypothalamus and the hypophysis.

REID, New Brunswick, N. J.

THE CENTRAL NERVOUS SYSTEM OF WINGED BUT FLIGHTLESS DROSOPHILA MELANOGASTER: AN EXPERIMENTAL STUDY OF THE RELATION BETWEEN MOTOR ABILITY AND NEUROMORPHOGENESIS. M. E. POWER, J. Exper. Zool. **115**:315 (Nov.) 1950.

The central nervous system of several mutant stocks of Drosophila melanogaster which have wings but are flightless were studied (*a*) to determine whether there is a morphogenetic correlation between the central nervous system and a serious motor deficiency, (*b*) to observe the degree of morphogenetic lability of the central nervous system, and (*c*) to study the mechanism of action of those genes which effect behavior patterns.

Most of the specimens were fixed as mature pupas and were cut in serial sections, impregnated with activated strong protein silver (protargol®) and toned with gold chloride. The volumetric data were obtained from planimeter measurements of camera lucida drawings of the sections through the thoracicoabdominal nervous system.

From the data, Power concludes that there are no detectable qualitative modifications in the central nervous systems of the flightless Drosophila. The inability to fly is not correlated with a quantitative hypoplasia within the thoracicoabdominal nervous center. There is no correlation between the area of the mutant wings and the amount of development of the thoracicoabdominal nervous system; even when vestigial the nervous system is fully developed. The mutant wings bear the same sense organs as those found in the wild type of animals.

This study failed to discover the mode of action of the genes which are associated with flightlessness. No clue was revealed as to the cause of flightlessness.

REID, New Brunswick, N. J.

FUNCTIONAL REGULATION IN FUNDULUS HETEROCLITUS EMBRYOS WITH ABNORMAL CENTRAL NERVOUS SYSTEMS. JANE M. OPPENHEIMER, J. Exper. Zool. **115**:461 (Dec.) 1950.

The central nervous system of Fundulus heteroclitus embryos was made abnormal by transplantation of material from the germ ring, or embryonic shield, into the prospective nervous system at the gastrula stage. The development of the behavioral pattern was observed in 50 experimental animals. In some embryos the grafts showed differentiation of brain structures confluent with those of the host; in others, their presence resulted in the suppression, rearrangement, or duplication of brain parts in the host.

The degree of functional regulation differed considerably among the individual embryos. While in some there were disturbances of locomotor, postural, and righting reflexes, or abnormalities in coordination of eye or mouth and branchial movements, in others functional regulation was complete.

In some embryos deficits in behavior could be correlated with specific rearrangements of visible structure pattern, but in others no such correlation was apparent. In general, the disturbance of behavior did not appear to be commensurate with the morphological disturbance in the central nervous system.

Oppenheimer concludes that the developing central nervous system can integrate more than the usual amount of material into an orderly functioning whole. Its fundamental pattern of organization allows considerable regulability. The nature of that pattern of organization, and of the factors responsible for its regulability, awaits further experimental analysis.

REID, New Brunswick, N. J.

SURGICAL LESION OF THE GENICULATE GANGLION FOLLOWING RETROGASSERINE NEUROTOMY: SENSORY INNERVATION OF THE EXTERNAL CANAL. F. D'AJUTOLO, Riv. oto-neuro-oftal. **26**:103 (March-April) 1951.

D'Ajutolo reports the case of a nun aged 54 in whom the geniculate ganglion was cut during an operation for trigeminal neuralgia on the left side, performed by the transtemporal route. During the operation the facial nerve, the geniculate ganglion, and motor and sensory fibers of the fifth cranial nerve were excised on the left side, with resultant peripheral facial paralysis, impairment of taste of the anterior two-thirds of the tongue, and a reaction of degeneration. No sensory changes for touch, pain, temperature, or the faradic current were found in the external ear, the retroauricular region, or the posterior and inferior portions of the external auditory canal. The author concludes that the geniculate ganglion has nothing to do with sensory innervation in these areas, contrary to the hypothesis of Ramsay Hunt, who based his views entirely on observations during the course of herpes zoster.

N. SAVITSKY, New York.

Physiology and Biochemistry

FORCED CIRCLING MOVEMENTS (ADVERSIVE SYNDROME): CORRECTION WITH DIMENHYDRINATE ("DRAMAMINE"). M. SCHIFF, W. G. ESMOND, and H. E. HIMWICH, Arch. Otolaryng. **51**:672 (May) 1950.

The authors subjected to study a syndrome including compulsive circling, caused by intracarotid injection of diisopropyl fluorophosphate, in order to analyze the underlying mechanism. Both peripheral and central elements were evaluated. Though the syndrome may be evoked by changes in vestibular receptors, as illustrated by the effects of cocainization, when diisopropyl

fluorophosphate was used locally in the ear, the characteristic behavioral changes could not be aroused in either rabbits or cats. The application of this drug to the round window or its direct injection into perilymph failed to evoke forced circling. These experiments, therefore, indicate that the vestibular receptors are not primarily involved in the syndrome as induced by diisopropyl fluorophosphate. They also suggest that the vestibular receptors are not cholinergic.

In contrast, the central portion of the mechanism is stimulated by diisopropyl fluorophosphate, which presumably allows the existence of an excess of acetylcholine in the brain, and the resulting abnormal behavior is corrected by atropine. Dimenhydrinate, which exhibits atropine-like properties, is effective against the excessive acetylcholine. The authors suggest that this atropine-like action, exerted on subcortical structures, is the basis for the therapeutic influence of dimenhydrinate on this syndrome. In any event, the experiments demonstrate that dimenhydrinate and diphenhydramine hydrochloride prevent compulsive turning in rabbits when administered before diisopropyl fluorophosphate and correct and abnormal behavior when given after it.

ALPERS, Philadelphia.

STIMULATION AND STRYCHNINIZATION OF SUPRACALLOSAL ANTERIOR CINGULATE GYRUS. R. H. DUNSMORE and M. A. LENNOX, J. Neurophysiol. **13**:207 (May) 1950.

By physiological neuronography the authors have confirmed the work of others that fibers from the anterior cingulate gyrus project to areas in the vicinity of Areas 31, 32, 6a, and 4S. In addition, they also found the transmission of strychnine spikes to areas in the presumptive location of Areas 8S, 2S, and 19S.

Electrical stimulation of the anterior cingulate gyrus was carried out in cats and monkeys, and the following effects were observed: (1) atypical motor movements; (2) arrest of motor movements; (3) arrest of respiration, and (4) electroencephalographic changes. All these effects occurred independently of one other.

The electroencephalographic effects were of four types: (1) suppression of strychnine spikes (ipsilateral); (2) suppression of spindles (ipsilateral); (3) suppression of spontaneous electrocortical activity (bilateral); (4) production of a seizure discharge (ipsilateral or bilateral). All these electroencephalographic effects occurred independently of one another.

The independent occurrence of the effects of stimulation of the anterior cingular gyrus suggests that they are mediated by independent pathways. The results of Dunsmore and Lennox would indicate that suppression of strychnine spikes, suppression of spindles, and arrest of motor movements are mediated via the caudate nucleus (not necessarily the same part).

ALPERS, Philadelphia.

EXPERIMENTAL PRODUCTION OF CONVULSIVE SEIZURES. C. L. ANDERSON, J. Nerv. & Ment. Dis. **109**:210 (March) 1949.

Anderson investigated the association between convulsive seizures and changes in the cholesterols of the body by injecting intracranially into eight adult rabbits equal parts of acetone and isotonic sodium chloride solution on alternate days. Each injection produced a convulsive seizure within 5 to 15 seconds, and three animals had seizures between injections. Analysis of the brains to determine the solvent effect of acetone indicated a statistically significant difference in the fat content of the treated brains and that of the controls. The author concludes tentatively that the convulsions were due to the fat-solvent effect of the acetone and that seizures between injections may have been due to the reduced lipin and lipid content of the brain.

FARMER, Philadelphia.

EFFECT OF α: β-DIHYDROXY-γ-(2-METHYLPHENOXY)-PROPANE (LISSEPHEN®) ON EXCITATION OF THE MOTOR CORTEX AND CONDUCTION THROUGH THE PYRAMIDS. ISIDORE FINKELMAN, and NORMAN B. DOBIN, J. Nerv. & Ment. Dis. **109**:323 (April) 1949.

Finkelman and Dobin studied the effect of mephenesin (lissephen®) on 12 cats by stimulating an area of the cortex with strychnine and detecting the conduction of impulses through the exposed pyramids with the aid of an electron tube amplifying system. Before the intravenous

injection of mephenesin, strychnine spikes were recorded from both cortex and pyramids. After injection, cortical spikes continued, but pyramidal spikes and movements of corresponding extremities disappeared. The authors conclude that mephenesin, in diminishing activity or producing impedance, acts upon subcortical efferent pathways.

FARMER, Philadelphia.

ACTION OF α: β-DIHYDROXY-γ-(2-METHYLPHENOXY)-PROPANE (LISSEPHEN®) ON PERIPHERAL NERVES. I. FINKELMAN and A. J-ARIEFF, J. Nerv. & Ment. Dis. **109**:326 (April) 1949.

Finkelman and Arieff investigated the effect of mephenesin (lissepheñ®) on the sciatic nerve and corresponding muscles in eight cats and six frogs. Mephenesin produced no significant change in the rheobase, chronaxie, galvanic tetanus ratio, or repetitive stimuli ratios, even when toxic doses were administered. Similar experiments with chondodendron tomentosum extract, purified (intocostrin®), caused a definite increase in rheobase and the threshold for repetitive stimuli, but the chonaxie was usually unaltered. The authors conclude that mephenesin does not act on the myoneural junction, as does curare.

FARMER, Philadelphia.

Neuropathology

EXPERIMENTAL STUDIES IN ALLERGIC ENCEPHALOMYELITIS: PREVENTION AND PROTECTION. A. FERRARO, L. ROIZIN and C. L. CAZZULLO, J. Neuropath. & Exper. Neurol. **9**:18 (Jan.) 1950.

The first object of this presentation is to emphasize once more that immunological reactions of the allergic type are likely to generate a histopathological process characterized principally by an inflammatory and vascular reaction. The second object is to emphasize the already known fact that through allergic mechanisms one can produce experimentally a patchy or diffuse demyelination closely resembling that encountered in some acute and chronic human demyelinating diseases, the closest analogy being found in acute disseminated encephalomyelitis. The third object is to present a summary of the authors' findings in relation to prevention of experimental allergic encephalomyelitis in guinea pigs.

Three methods of protection, using emulsions of normal brain, were employed prior to injection of the emulsion-producing disease. It was found that all groups of protected animals disclosed a definitely higher number of survivors. The nature of this protective action of normal brain tissue is still unknown.

Other work was done in an attempt to produce encephalomyelitis with emulsions of several extracts of sheep brain. The authors were able successfully to produce a predominantly allergic meningitis with the acetone and ether extracts of brain tissue. The residue, consisting mostly of proteins, seems to be the most active agent in the production of the allergic encephalomyelitis.

There is definite indication that some of the brain components taken separately possess antigenic properties capable of causing encephalomyelitis, and yet not comparable to the strong antigenicity of the total brain.

ALPERS, Philadelphia.

EXPERIMENTAL CONGENITAL TOXOPLASMOSIS: IV. GENITAL AND SECONDARY LESIONS IN THE MOUSE INFECTED WITH TOXOPLASMA BY THE VAGINAL ROUTE. D. COWEN and A. WOLF, J. Neuropath. & Exper. Neurol. **10**:1 (Jan.) 1951.

Cowen and Wolf studied the character and spread of infection of the genital tract with Toxoplasma in the adult mouse as revealed by postmortem examination of its tissues. The pathologic observations are based on the postmortem examination of 302 mice infected by the vaginal route. For the entire series, the duration of life after the first exposure to Toxoplasma varied from 3 days to 11 weeks, but the majority of the animals were examined 2 to 4 weeks after the initial inoculation.

It was found that primary inflammatory lesions developed in the vaginal wall of mice three to five days after the introduction of Toxoplasma into the vagina. After a further interval of six to eight days, specific focal inflammatory and necrotizing lesions appeared in distant organs, most constantly the central nervous system, lungs, and heart. The secondary lesions had the

pathologic characteristics of a blood-disseminated infection and resembled those seen in animals inoculated by other peripheral routes.

The lesions in the nervous system consisted of small foci of inflammation, associated with varying degrees of degeneration of parenchymal elements. Lymphocytes, large mononuclear cells, and polymorphonuclear leucocytes constituted the majority of the cells in the exudate, with an increase of the last-named type in the more acute lesions and in the presence of necrosis. In animals which survived the first few weeks of infection there was a distinct tendency for the pathologic process to subside in intensity and to become histologically "chronic." In the nervous system, calcification of healed lesions was occasionally seen. Parasites were more numerous in the early lesions. They progressively decreased in number as the acute stages were passed.

Cowen and Wolf found no tendency for the infection to ascend directly from the vagina into the upper part of the genital tract. The pathologic observations suggested that the parasitemia and generalized toxoplasmosis developed during the earlier phases of the vaginitis and that the vagina did not constitute a focus of chronic infection from which toxoplasmas might continue to be disseminated or expelled. Parasites were present in the early vaginal lesions but were not seen in histologic sections after the 19th day of the disease. Histologically demonstrable toxoplasmas persisted in the brain as "cysts" for many weeks without progression or reactivation of the infection in this organ or elsewhere.

ALPERS, Philadelphia.

TRANSPLANTATION OF HUMAN BRAIN TUMORS INTO ANIMAL HOSTS. J. MARTIN, J. Neuropath. & Exper. Neurol. **10**:40 (Jan.) 1951.

Martin reports on the results of implantation of fresh specimens of human brain tumor (and other neural and non-neural tumor) tissue into animal hosts, with a study of the macroscopic growth changes, as well as of the microscopic picture at the site of implantation.

Eighty-eight cerebral tumors of all histologic types, obtained at operation, were transplanted into 145 animals. As a means of securing control data, 41 non-neurogenic tumors were obtained at operation and transplanted into 95 animals. For further observation on the various local reactions to implantation, 20 animals were used for the implantation of cat placenta, adult human endometrium, and other cat and guinea pig tissues.

Bits of these various tissues were placed in the subarachnoidal and ventricular spaces, in the white matter of the cerebrum, in the tunica vaginalis of the testis, in the Fallopian tube, under the sciatic sheath, and, in the great majority of animals, in the anterior chamber of the eye. A saline suspension of tumor cells was also injected directly into the carotid artery.

When growth of the implant of whatever type proved possible, such growth occurred only in the anterior chamber of the guinea pig eye. The vast majority of the implants were eventually absorbed, and the anterior chamber became completely clear or with a mirror cloudiness, due to a field of fibroblastic reaction. Several testicular, ovarian, and placental implants remained vascularized and viable for several months; but they failed to expand beyond their original bulk, and from them retransplantation to successive generations of animals was not successful. As though to indicate their ability to exist in new surroundings, intracranial metastatic nodules of non-neurogenic tumors gave the best results. Two metastatic carcinomas and two metastatic sarcomas have gone into the fourth transplant stage. One heavily melanotic sarcoma of the spinal cord, having arisen from a pigmented mole of the skin, failed to show melanin in either the second or the third generation transplant, though the appearance of the tumor cells otherwise appeared unchanged from generation to generation. Next in ability to proliferate and persist in serial transplantations were the microscopically more malignant sarcomas and carcinomas. Least likely to grow in transplantation were the primary neurogenic tumors. One glioblastoma and two medulloblastomas, apparently growing after two months in the anterior chamber of guinea pigs, failed to proliferate when transplanted to a second animal. In no instance did a meningioma, hypophyseal adenoma, or other primary tumor of the brain or spinal cord survive primary transplantation.

It is apparent from this large group of neurogenic tumors, transplanted into animal hosts, that survival and proliferation of the tumor under standardized conditions is the rare exception, rather than the rule. This is not unexpected, since it is generally recognized that tumors of neural origin do not follow all the rules of growth conduct of non-neurogenic tumors, either clinically or in animal transplantation.

It has been questioned whether such conduct of neural tumors, both clinically and experimentally, is an indication of a special lack of autonomy on their part. It would seem that, at least so far as the matter of transplantation is concerned, failure to grow under such conditions does not speak for such lack of autonomy, for even the non-neurogenic tumors have for the most part, by comparison, only a narrow margin of autonomy sufficient for survival in transplanted form in certain instances.

ALPERS, Philadelphia.

PATHOLOGY OF ACUTE ALCOHOLISM. W. O. UMIKER, U. S. Nav. M. Bull. **49**:744 (July-Aug.) 1949.

According to Umiker, fatal, uncomplicated, acute poisoning due to alcohol is uncommon. Only three cases were found in a series of well over 1,000 unselected necropsies at the United States Naval Hospital, Bethesda, Md. These cases are reported. It is not easy to consume a dose of alcohol that will prove fatal. In the usual bout of heavy drinking the participant loses consciousness, and thereby the ability to consume more alcohol, before a lethal dose is taken. Nevertheless, acute alcoholism, with its resultant physical, mental, emotional, and moral deterioration, is the underlying factor in a large percentage of deaths. The drunken pedestrian stumbles in front of a bus; the intoxicated driver falls asleep at the wheel; the emotionally disturbed drinker takes his or another's life; the circulation in a stenosed coronary artery falters under the strain of acute alcoholism, or the Pneumococcus finds an easy victim. The pathologist often fails to consider the possibility of acute alcoholism, and the final diagnosis is made by the toxicologist, rather than by the pathologist. The most constant pathologic changes are severe meningeal and cerebral congestion, pulmonary edema, acute gastritis, visceral congestion, and acute pancreatic necrosis. Most of these changes are found in other conditions, especially those characterized by anoxemia. Postmortem determinations of the alcohol in the blood, urine, and tissues are of diagnostic value only when death has taken place within a few hours after the onset of the alcoholic coma. Acute alcoholism should be suspected as the cause in all cases of suicide, homicide, accidental trauma, and poisoning and as a complicating or precipitating factor in other medical or surgical fatalities.

J. A. M. A.

ALLERGIC ETIOLOGY OF INFLAMMATORY DISEASES OF THE NERVOUS SYSTEM. E. NIEDERMEYER, Wien. klin. Wchnschr. **61**:122 (Feb. 25) 1949.

Niedermeyer reviews extensively the German literature concerned with the role of allergy in neurological conditions. The anatomic and physiopathological bases of the allergic manifestations of the nervous system are discussed, with special attention to neuritides, Quincke's edema (angioneurotic edema) of the brain, benign lymphocytic choriomeningitis, and certain encephalitides. The albuminocytologic dissociation, the fleeting symptoms, and the occurrence of conditions after an incubation period of a duration similar to that of serum sickness are held to favor the allergic origin. The author emphasizes the non-neurotropic nature of many of the pathogens and expresses the view that one is dealing with a serous response caused by antigen-antibody interaction.

Two cases are reported to illustrate these views. One was a case of benign lymphocytic choriomeningitis in which local dental foci were found and a history of polyarthritis was obtained. In the other case, with autopsy report, the diagnosis was meningoencephalomyeloradiculitis, and the impression of an allergic origin was based on the presence of tonsillar foci and ascariasis; an allergic predisposition is also predicated in this case on the basis of a history of eczema.

MASON, New York.

Psychiatry and Psychopathology

SOME OBSERVATIONS ON A FORM OF PROJECTION. L. J. SAUL, Psychoanalyt. Quart. **16**:472 (Oct.) 1947.

Saul points out that some people treat other persons chiefly as projections of certain of their own unconscious trends, just as they represent these trends in dreams by various types of persons. The author, by the use of illustrative case material, calls attention to further distinctions, namely, to what trends are projected, to which objects, and to the reactions of the ego to the projected

trends (hate, fear, idealization, love, etc.). The illustrations given are from bisexuality; for example, a man may hate and fear a woman because to him she represents a projection of his own poorly repressed feminine trends, which are hated and feared. From another viewpoint, such a man would react in this way to women because the women stimulate the femininity which he hates and fears in himself. According to the author, this is a possible reason that it is so difficult for men to understand women.

Saul points out that this form of projection, that is, treating other persons as projected parts of one's own unconscious, is widely, if not, universally seen, at least in some degree.

WERMUTH, Philadelphia.

Meninges and Blood Vessels

MENINGITIS DUE TO PSEUDOMONAS AERUGINOSA TREATED WITH POLYMYXIN B. E. R. HAYES, and E. YOW, Am. J. M. Sc. **220**:633 (Dec.) 1950.

Meningitis due to Pseudomonas aeruginosa (Bacillus pyocyaneus) is often attributable to introduction of the organism during spinal puncture. The mortality is at least 55%. Polymyxin isolated from Bacillus polymyxa, is active against Gram-negative bacteria. A case of Ps. aeruginosa meningitis following spinal anesthesia is reported, in which the condition resisted therapy with sulfadiazine, aureomycin, penicillin, and streptomycin, the last two drugs being given by the intramuscular and intrathecal routes. Polymyxin B given intramuscularly and intrathecally produced a sterile spinal fluid in one day. Two recurrences of the meningitis after cessation of treatment were both controlled by the same therapy. The side-reactions of the intrathecal injections consisted of nausea and vomiting, pruritus, and pains in the legs.

BERLIN, New York.

TORULOSIS OF THE CENTRAL NERVOUS SYSTEM: REVIEW OF LITERATURE AND REPORT OF FIVE CASES. W. H. MOSBERG and J. G. ARNOLD, Ann. Int. Med. **32**:1153 (June) 1950.

Cryptococcic meningitis (torulosis) is a chronic inflammatory disease due to invasion of the central nervous system by the fungus Cryptococcus neoformans. This disease presents a protean neurological picture. The diagnosis of cryptococcic meningitis cannot be made on a basis of signs and symptoms. The disease may be confused with brain tumor, subarachnoid hemorrhage, subdural hematoma, brain abscess, encephalitis, and meningitis of pyogenic, syphilitic, tuberculous, or virus origin.

The antemortem diagnosis of cryptococcic meningitis can be made only by examination of the cerebrospinal fluid, and even the cerebrospinal fluid findings are inconstant. Before the diagnosis can be made, the organism must be identified in the cerebrospinal fluid, either by direct examination or by culture. To make a clinical diagnosis of torulosis, one must at all times be aware of the disease. Torulosis should be suspected whenever an unexplained pleocytosis is present. The diagnosis will seldom be missed if routine cultures are made on Sabouraud's medium and observed for one month.

Five cases of torulosis of the central nervous system are here reported by Mosberg and Arnold, in four of which the diagnosis was made ante mortem. One of the patients survived 38 months after the onset of symptoms, and autopsy showed no evidence of torulosis. In another the torulosis was associated with moniliasis.

The authors present an analysis of therapeutic agents which have been employed in the 172 cases of torulosis reported to date. As yet no method of treatment has proved effective.

ALPERS, Philadelphia.

VERIFIED CEREBRAL ANEURYSM WITH NEGATIVE ARTERIOGRAM. BERNARD J. ALPERS and JAMES J. RYAN, J. Nerv. & Ment. Dis. **109**:220 (March) 1949.

Alpers and Ryan report two cases of cerebral aneurysm in which the arteriogram was noncontributory. In the first case, chronic intermittent frontal headaches were replaced by severe vertex headaches and pain in both eyes. This condition became associated with blurred vision in the right eye, diplopia, and paralysis of the right internal rectus and the right superior levator. Sudden excruciating pain developed in the vertex and radiated down the neck between the

shoulders. This history, with a syndrome of complete ptosis of the right eyelid, outward rotation of the right eyeball, a dilated, inactive right pupil, and bilateral early papilledema, led to a diagnosis of extramedullary compression of the right oculomotor nerve. Meningioma or aneurysm of the posterior communicating artery was considered. The arteriogram revealed no lesion; the pneumoencephalogram was normal except for absence of air in the chiasmal cistern. In the second case, the patient awakened with partial ptosis of the left eyelid, and this became complete within one week. Examination revealed a dilated, inactive left pupil and paralysis of upward, downward, and inward movements of the left eye. The tentative diagnosis was that of aneurysm of the left internal carotid or the posterior communicating artery, but the arteriogram offered no diagnostic confirmation.

Operation disclosed an aneurysm in both cases. The authors state that a history of recurrent unilateral head pain or pain behind and over the eye should suggest cerebral aneurysm, particularly if the pain is followed by ocular paralysis and/or loss of visual acuity, diplopia, facial pain, dysphonia, dysphagia, or other cranial nerve involvement.

FARMER, Philadelphia.

ARTERIOGRAPHY AND CAROTID ARTERY LIGATION IN INTRACRANIAL ANEURYSM AND VASCULAR MALFORMATION. I. S. WECHSLER, S. W. GROSS, and I. COHEN, J. Neurol., Neurosurg. & Psychiat. **14**:25 (Feb.) 1951.

The authors report the results of ligation of the common carotid artery in the neck in 30 cases, including 17 cases of aneurysms of the circle of Willis, 9 cases of vascular malformations of the hemisphere, and 4 cases of carotid artery-cavernous sinus fistulas.

In the group with malformations no death occurred; in one case hemiparesis developed. In no case did bleeding recur after operation. Two patients continued to have convulsions. In the group with aneurysms there was one death nine hours after ligation. The other deaths in this group followed craniotomy, one after 10 days and one after 4 weeks. There was no recurrence of bleeding. There was one postligation hemiplegia with aphasia.

The authors feel that the mortality, morbidity, and results of this method of treatment compare favorably with those of other methods advocated for these conditions.

ALPERS, Philadelphia.

COEXISTING TUBERCULOUS AND MENINGOCOCCAL MENINGITIS: REPORT OF CASE. E. A. RILEY, New England J. Med. **239**:386 (Sept. 9) 1948.

Riley presents a history of a man aged 26. What at the onset appeared to be uncomplicated meningococcic meningitis terminated fatally with a tuberculous infection of the meninges, and was further complicated by the recrudescence of a malarial infection that the patient had contracted during his service in Sicily and Italy. The author reviews the literature, collecting cases that have been reported since 1911. Most of these case reports are from the foreign literature. The case reported here is the first to be reported from American sources, and is approximately the 34th case of its type in the literature. The source of the tuberculous meningitis in the author's case remains a mystery. No visceral focus of tuberculosis was found in any of the organs examined. The clinical and pathologic evidence in the reported case suggests that the meningococcic infection may have activated a latent tuberculous focus.

J. A. M. A.

TREATMENT OF HEMOPHILUS INFLUENZAE B MENINGITIS: REPORT OF 67 CASES. K. J. McMORROW and F. H. TOP, Pediatrics **5**:452, 1950.

McMorrow and Top report on 38 boys and 29 girls with meningitis caused by Hemophilus influenzae type B who were admitted to the Herman Kiefer Hospital, in Detroit, during the period from January 1943 to September 1948. Thirty-three patients were less than 2 years of age, and 11 of the 17 patients who died belonged to this age group, thus accounting for 65% of the deaths. The corrected fatality rate for the group under 2 years of age is 18.2%, obtained by disregarding patients who died within 36 hours of admission and patients admitted to the hospital after 21 days of illness. Thirty-seven patients were treated with sulfadiazine and serum; 5, with sulfadiazine and streptomycin; 18, with sulfadiazine, serum, and streptomycin, and 4, with sulfadiazine alone; 2 did not receive specific treatment. The four patients admitted and treated at the end of the third week of illness died. Both deaths in the patients under 2 years of age

who received sulfadiazine, serum, and streptomycin occurred in children who had been ill three weeks before receiving treatment. The prognosis is likely to be unfavorable in the age group under 2 years if treatment is delayed beyond the 14th day. The fatality rate for patients who received sulfadiazine and serum was the same as that for patients who received streptomycin in addition. Serum therapy proved ineffective in the age group under 2 years when delayed beyond the 14th day of illness. The intravenous route for administration of serum offers no advantage over the intramuscular route with respect to prognosis.

J. A. M. A.

SIGNIFICANCE OF CONVULSIONS IN CHILDREN WITH PURULENT MENINGITIS. C. OUNSTED, Lancet **1**:1245 (June 9) 1951.

Ounsted reports on 90 consecutive cases of purulent meningitis in children in which he found that there is a close association between the occurrence of fits and the outcome of the disease. The chief causative organisms were Meningococcus, Hemophilus influenzae, Pneumococcus and a hemolytic Streptococcus type B. All the children were given adequate chemotherapy, but 18 died or were left with gross cerebral damage, a failure rate of 20%. Thirty-seven children (41%) had fits in the course of their illness. In this group of children with fits the failure rate was 43%, whereas in the group who were free from fits the failure rate was 4%. The failure rate was also higher for those children who had multiple fits than for those with a single convulsion. The younger the child, the greater was the tendency for seizures to develop. Seizures that occurred after the institution of hospital treatment were more ominous than those limited to the early days of the disease. Phenobarbital was tried prophylactically, and the rate of cure was decidedly higher in this group, with a corresponding decrease in the number of seizures. Of eight patients in whom status epilepticus developed, seven died. The author found intramuscular administration of amobarbital sodium to be of great help in controlling the patients with seizures.

Ounsted concludes that when convulsions are prevented or do not occur, recovery follows in 96% of cases and that routine prophylaxis with phenobarbital is safe and may lead to a reduction in the mortality.

MADOW, Philadelphia.

SPONTANEOUS RECOVERY IN A CASE OF TRAUMATIC PULSATING EXOPHTHALMOS: IMPORTANCE OF RETINAL AND CEREBRAL HEMODYNAMICS. GIUSEPPE DI LUCA, Riv. oto-neuro-oftal. **24**:267 (May-June) 1949.

Of 500 cases of pulsating exophthalmos in the literature, recovery was spontaneous, without treatment, in 5.4%. A woman aged 24 fell off a bicycle in 1940, sustaining two fractures in the right occipital region, cerebral concussion, and paresis of the left side of the face, which lasted two or three days. After discharge she complained of occasional diplopia, with vertical position of images, and occasional headache. Soon after she noticed noises in the head, which were synchronous with the heart beat. One year after the accident her family observed that the right eye was more prominent and was congested. On her admission, the right eyeball was prominent; the conjunctival veins were dilated, and there was chemosis. No ocular palsy was seen, and diplopia was not detected, even with the Maddox rod. Exophthalmometric readings were 23 mm. in the right eye and 13 mm. in the left eye; on palpation there was a slight orbital pulsation, which was synchronous with the pulse. A bruit was heard in the region of the right eye, which was also synchronous with the pulse. The bruit disappeared when the right carotid artery was compressed in the neck. The right disk was hyperemic, with slightly dilated veins in the right fundus. The intraocular tension was 24 mm. Hg in the right eye and 20 mm. in the left eye; the blood pressure was 110/60. A shadow was noted in the region of the sphenoidal fissure on the right side; she refused to have ligation of the carotid artery.

The patient remained about the same for two years, but three months before she was seen again she suddenly lost consciousness for about 15 minutes. She was dizzy and had impairment of vision for another 15 to 20 minutes. Soon after that there was decided improvement, with disappearance of the bruit and rapid recession of the exophthalmos and injection of the right eye. One year later, there was no injection of the vessels; exophthalmos was 16 mm. in the right eye and 13 mm. in the left eye; roentgenograms of the skull showed no shadow in the region of the right orbital apex. The patient was last seen one month later, when exophthalmometric

readings were 16 mm. on the right and 13 mm. on the left. Examination otherwise revealed nothing unusual.

The author believes that the increased intraocular pressure was due to a tendency to chronic glaucoma, which in turn, was intensified by the increased intraocular pressure. The author believes that the spontaneous improvement was due to thrombosis at the site of the fistula, between the artery and the vein. He also notes the pathognomonic syndrome of pressure of retinal vessels in pulsating exophthalmos, lowering of the systolic retinal pressure, and increase of the retinal venous pressure. When the retinal diastolic pressure drops more than 50% with digital compression of the carotid artery, ligation is dangerous. If this drop is between 20 and 50%, closure of the artery should be gradual.

N. SAVITSKY, New York.

WINTER HEADACHES. G. MURPHY, Prensa méd. argent. **37**:2995 (Dec.) 1950.

Murphy reports three cases of headache after exposure to cold. Two of the patients were women, aged 18 and 34, and one, a man, aged 28. The headaches were usually frontal, occasionally occipital, and continued to recur for six, four, and two years, respectively. In all cases the head had to be covered for relief on exposure to cold; the headaches were less severe during warm weather. In one case the winter headaches were associated with migraine, and in another there was prompt relief with ergotamine tartrate. One of the women had a definite history of allergy to cold; her cold allergy and the winter headache cleared up with antihistaminic treatment. One patient had asthma. The author believes that these headaches are due to extracerebral arterial dilatation on the basis of cold allergy.

N. SAVITSKY, New York.

NONPULSATILE UNILATERAL EXOPHTHALMOS CAUSED BY ANEURYSM OF THE OPHTHALMIC ARTERY. J. SVERDLICK and A. A. VEPPO, Prensa méd. argent. **38**:629 (March 16) 1951.

A white man aged 54 was first seen on Oct. 3, 1948. On June 10, 1948, he awoke with a severe pain in the left eyeball. This was associated with a subconjunctival hemorrhage, which lasted 10 days. Soon afterwards he began to complain of double vision, dizziness, and severer pain in the left eyeball. On Aug. 25 the left eyeball began to protrude, and vision diminished in the left eye and to some extent in the right eye. Noises in the head, described as similar to escaping steam, became intense and continuous.

Examination revealed a bruit in the left temple, which disappeared with compression of the carotid artery. The results of the neurologic examination were negative. The right eye showed papilledema and definite arteriosclerosis, with visual acuity of 10/10. The left eye showed pronounced exophthalmos (30 mm.), but the eyeball did not pulsate, was reducible, and was directed downwards and inwards. There were intense chemosis in the inferior part of the conjunctiva and congestion of the vessels in the anterior pole of the eye. The pupil was mydriatic and fixed to light and in accommodation. Visual acuity in the left eye was 2/10, and there was paralysis of the right external rectus. On the left side there was 3 D. of papilledema with hemorrhages.

Injection of iodopyracet solution (diodrast®) into the carotid artery showed an aneurysm of the left ophthalmic artery. On Oct. 22, 1948, the left internal carotid artery was ligated. Except for transitory mild difficulty with speech, there were no sequelae. The patient noted the disappearance of the head noises immediately after the ligation. On Nov. 9, 1948, there was no exophthalmos; the left pupil reacted to light and in accommodation and was of normal size; the papilledema was regressing, and vision had returned to normal. The patient was perfectly well two years later.

The author found only three other cases of pronounced dilatation of the ophthalmic artery associated with ocular changes. This case is the only one in which ligation of the carotid artery was the only therapeutic procedure.

N. SAVITSKY, New York.

MENINGITIS DUE TO AEROBACTER IN A NEWBORN CHILD 4 DAYS OLD. P. REFINETTI, J. B. DOS REIS, and R. AIDAR AUN, Arq. neuro-psiquiat. **7**:299 (Sept.) 1949.

A 4-day-old boy cried inordinately for 12 hours and refused the breast. Examination revealed a slight icteric tinge, and the temperature was 36.6 C. (97.9 F.); the fontanel was tense, and crying was increased when the child's head was flexed. The Kernig and Brudzinski signs were

not elicited; there were a red throat and bilateral otitis media, for which the drum membranes were incised. The child was placed under treatment with sulfadiazine immediately. He had three attacks of tremulousness and cyanosis during the night. A lumbar puncture was done a day later. The fluid was turbid, and the child was placed under penicillin therapy. Gram-negative organisms were found the next day, and intrathecal and intramuscular administration of streptomycin was added. The child did poorly in spite of the treatment with sulfadiazine, penicillin, and intrathecal, intramuscular, and intraventricular injection of streptomycin. During the course of the illness a complicating ventriculitis apparently developed, because, as the lumbar fluid cleared somewhat, the ventricular fluid showed increased cells and protein. After the first puncture the fluid continued to be hemorrhagic. The child did poorly and died after 17 days of illness. The authors point out the rarity of infection by Aerobacter in the newborn and emphasize the importance of culturing hemorrhagic fluids, especially of the newborn. They also stress the paucity of signs and objective findings in newborn children. The child died of hydrocephalus, probably due to ventricular block. Histologic examination of the brain showed evidence of meningoencephalitis; brain abscess was not found.

SAVITSKY, New York.

Diseases of the Brain

AN OCULOKINETIC TEST OF EQUILIBRATORY CO-ORDINATION HAVING DIFFERENTIAL DIAGNOSTIC USE. RUSSELL MEYERS, J. Nerv. & Ment. Dis. **109**:226 (March) 1949.

Meyers describes a clinical test for defect in equilibratory coordination as follows: The patient assumes the tandem-stance posture, with the right foot forward and with his weight maintained mainly on the left foot. He then fixates on the examiner's finger about 2½ ft. (45 cm.) in front of his own nose and follows the examiner's finger through an arc of 35 degrees to the right and then to the left. The entire process is repeated with the position of the patient's feet reversed. The author states that the test is more sensitive than the Romberg test or the tandem-stance test and that the test possesses some merit in differentiating supratentorial and infratentorial lesions. In cases of supratentorial lesions, the direction of postural deviation is usually contralateral, whereas in cases of infratentorial lesions the deviation is ipsilateral.

FARMER, Philadelphia.

AMYTROPHIC LATERAL SCLEROSIS. A. P. FRIEDMAN and D. FREEDMAN, J. Nerv. & Ment. Dis. **111**:1 (Jan.) 1950.

Friedman and Freedman report a series of 111 cases of amytrophic lateral sclerosis. There were 77 deaths with 50 autopsies. The average age of onset was 52, and the incidence of the syndrome among patients admitted with neurologic diseases was 3.3%. Men were affected twice as frequently as women. In only 11 cases was there any associated congenital defect. There was no instance of neurologic disease in relatives except that amytrophic lateral sclerosis occurred in one pair of siblings in the series.

In 98% of the cases clinical evidence of involvement of the anterior horn cells was presented; in 25% there were no clinical signs of pyramidal-tract involvement, but degeneration of the pyramidal tracts was always noted at autopsy. In 50% of the group there were subjective sensory symptoms, and in 10% objective sensory signs. Mental changes were noted in 33% at some time during the disease. Laboratory findings were as a rule normal; the average spinal fluid protein was 39 mg. per 100 cc. In 38% of the group the first complaint was of difficulty with the lower extremities; in 31%, of difficulty with the upper extremities, and in 21%, of bulbar symptoms.

FARMER, Philadelphia.

Diseases of the Spinal Cord

TRAUMATIC CORDOTOMY. H. E. LEFEVER, Dis. Nerv. System **9**:347 (Nov.) 1948.

LeFever describes two cases in which gunshot wounds of the spine resulted in discrete section of the lateral spinothalamic tract. One patient evidently had injury to the pathway high in the cervical portion of the cord, with subsequent selective analgesia and thermoanesthesia on the opposite side of the body below the level of trauma. In the second patient both lateral spino-

thalamic tracts were severed in the upper dorsal region, and loss of pain and temperature perception was demonstrated below the seventh thoracic dermatome. In both cases touch, pallesthesia, joint sense, two-point discrimination, and topognosia were everywhere intact, thus furnishing further clinical evidence of the separateness of the spinal cord pathway conveying pain and temperature impulses.

BEATON, Tucson, Ariz.

RUPTURED INTERVERTEBRAL DISK FROM POSITIVE ACCELERATION. R. S. SHAW, J. Aviation Med. **19**:276 (Aug.) 1948.

Shaw presents two instances of back injury appearing after exposure to positive acceleration. The first is a case of ruptured intervertebral disk proved at operation. The second, although not verified, presents the syndrome typical of ruptured disk. These cases have in common an awkward, flexed position of the back during a "pull-out." This is probably the reason that these men suffered injury from accelerations ordinarily considered well below the tolerance limit for back injury. Under positive acceleration this flexion would increase and result in severe strain on the posterior longitudinal ligament and its adjacent annulus fibrosus. At the same time the nucleus pulposus would be compressed and forced against these strained posterior supports. The likelihood of posterior herniation of the nucleus pulposis is great in these circumstances. The author stresses that it is advisable to maintain an erect spine during exposure to positive acceleration, whether in curvilinear flight or in the ejection seat.

J. A. M. A.

HYPOGLYCAEMIA FROM ISLET CELL TUMOR OF PANCREAS WITH AMYOTROPHY AND CEREBROSPINAL NERVE CELL CHANGES. M. J. TOM and J. C. RICHARDSON, J. Neuropath. & Exper. Neurol. **10**:57 (Jan.) 1951.

Tom and Richardson describe a case of islet cell tumor of the pancreas in which there developed a severe and fatal encephalopathy and myelopathy. The severe anoxic changes in the brain resulted in dementia, dysphagia, cortical visual disturbances, and terminal mild hemichorea. The unique and most interesting feature was a pronounced widespread degeneration of the ventral horn cells of the spinal cord, resulting in paralysis and wasting of distal limb muscles.

The name "hypoglycemic amyotrophy" might be suggested as a suitable one to describe the clinical and pathological nature of the lower motor neuron lesion. It is unlikely that this rare effect of severe hypoglycemia on ventral horn cells of the spinal cord will ever be encountered except in association with severe and prolonged cerebral changes.

ALPERS, Philadelphia.

ASYMPTOMATIC TRANSFIXION OF SPINAL CORD BY A KNIFE BLADE. RAFAEL CASTILLO and EDGAR A. KAHN, J. Neurosurg. **2**:179 (March) 1950.

Castillo and Kahn report the case of a man who carried on his normal activities for 23 years with his spinal cord transfixed by a knife blade.

The patient, aged 43, had been stabbed in the back 23 years previously. There was no immediate paralysis, pain, or other disability. Five weeks later he returned to work with only slight weakness of the left leg, which disappeared completely in three months. For the next 13 years he was asymptomatic. He then noted some incoordination in the left leg. Three years prior to his admission to the hospital he noted difficulty in attaining an orgasm, with increased stiffness and weakness of the left leg. There were no sphincteric difficulties.

Examination showed hypalgesia and hypesthesia to the fourth thoracic dermatome, being more pronounced on the left. He walked with a limp, with spastic monoplegia of the left leg. Roentgenograms showed a knife blade, 3 inches (8.6 cm.) in length, at the level of the fourth thoracic segment, lying just to the left of the midline.

Operation for removal of the foreign body was performed. The blade had entered the spinal cord in the midline, completely piercing it, and was embedded in the anterior part of the vertebral canal. It was surrounded by a dense cicatrix. The blade and scar were removed.

Immediately after operation the patient was able to move both legs, but they were rather spastic. Hypesthesia was present to the level of the fourth thoracic dermatome. There was transient retention of urine. Fourteen months later he walked without the use of a cane and had normal sphincteric control. The sensory findings and sexual function were unchanged.

TOZER, Topeka, Kan.

USE OF POSITIVE PRESSURE AS AID IN HANDLING RESPIRATORY PARALYSIS FROM ANTERIOR POLIOMYELITIS. R. L. MASLAND, R. B. LAWSON and W. M. KELSEY, J. Pediat. **36**:31 (Jan.) 1950.

Masland and co-workers used positive-pressure breathing in 10 patients with the respiratory or bulborespiratory forms of poliomyelitis during the 1948 epidemic in North Carolina. Severe pulmonary edema was reversed by the use of the positive-pressure respirator in three patients, and pulmonary edema was probably prevented in some of the other patients. The progressive hypoventilation which develops in the paralyzed patient is due in many instances to pulmonary edema, rather than to atelectasis. The intermittent use of positive-pressure breathing leads to improvement in patients of this type. Positive-pressure respiration has definite value in dealing with respiratory paralysis in poliomyelitis, both in increasing the ease of movement of the patient and in the prevention and treatment of certain of the pulmonary complications which develop in the paralyzed patient.

J. A. M. A.

CATABOLIC EFFECT OF TRAUMA OF THE SPINAL CORD AND ITS INVESTIGATIVE TREATMENT WITH TESTOSTERONE PROPIONATE: PRELIMINARY REPORT. I. S. COOPER, E. H. RYNEARSON, A. A. BAILEY, and C. S. MACCARTY, Proc. Staff Meet., Mayo Clin. **125**:326 (June 7) 1950.

This study was undertaken in an attempt to obtain an agent which might lessen the catabolism of body protein which is induced by injury of the spinal cord.

The protein-catabolic reaction was studied in six men after severe injury to the spinal cord. The severity of the injury was approximately the same in all six patients. The degree of catabolism of body protein in each case was determined by estimation of the daily loss of urinary nitrogen and by nitrogen balance studies. Two of the six men received testosterone propionate after spinal cord injury. The absolute degree of nitrogen waste was less pronounced in the two men who received testosterone propionate than in the four men who did not receive this drug.

ALPERS, Philadelphia.

THE VISUAL FIELD DEFECTS IN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD. G. H. H. BENHAM, J. Neurol., Neurosurg. & Psychiat. **14**:40 (Feb.) 1951.

The occurrence of optic nerve atrophy as part of the syndrome of subacute combined degeneration of the spinal cord is distinctly uncommon. The purpose of this communication is to record further observations on the fields of vision in this syndrome.

In a series of 112 cases of subacute combined degeneration, 5 instances of optic nerve atrophy were encountered; in 3 of these accurate assessment of the visual fields was possible, the essential defects being scotomas of the centrocecal type with varying degree of peripheral contraction.

ALPERS, Philadelphia.

SENILE MYELOPATHY. A. AUSTREGESILO, Rev. neurol. **80**:683 (Nov.) 1948.

Austregesilo differentiates senile myelopathy from arteriosclerotic and other forms found in old age. Clinically, the senile form is characterized by steady progression without acute exacerbations or remissions, such as would be caused by areas of infarction. Symptoms of fatigue, awkwardness, and slowness are more marked in the legs, where signs of pyramidal tract involvement predominate; sensory signs are likely to be minimal. Tremor is present in the late stages. Commonly confused is Parkinsonism, but the author believes that the selective severity of the condition in the leg suffices usually to differentiate it. The disturbance is made much worse by dietary and vitamin deficiency, which the author recommends be carefully treated in all cases.

LEGAULT, Washington, D. C.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

James L. Poppen, M.D., Presiding
Regular Meeting, April 18, 1951

Recurrent Cerebrovascular Symptoms of Vasospasm. DR. D. DENNY-BROWN.

The rationale of treatment of cerebrovascular accidents by stellate-ganglion block or by use of vasodilators depends on the concept of "vasospasm," either as a primary event or as a cause of delay in the establishment of collateral circulation. The type of disorder normally cited as exemplifying "vasospasm" is that of recurrent episodes of hemiplegia, monoplegia, or aphasia. Arteriography has shown that the usual cause of these episodes is chronic stenosis or occlusion of the internal carotid artery.

Eight cases had been studied at the neurological unit of the Boston City Hospital in the last two years, and examples were cited. Two cases of the similar syndrome of chronic stenosis of the basilar artery were also cited. When the cause of an episode could be identified, it was found to be related to a fall in systemic blood pressure (syncope, 1 case; use of a peripheral vasodilator, 1 case; gastrointestinal hemorrhage, 2 cases; sleep, 5 cases; myocardial infarction, 1 case). The use of stellate-ganglion block in a critical case, within 30 minutes of onset of symptoms, with well-maintained blood pressure, not only was totally ineffective, but was followed by persistence of the symptoms. This situation is the ideal test for the value of the procedure. It was concluded that in such crises of cerebral hemodynamics the collateral circulation is already maximally dilated.

DISCUSSION

DR. DONALD D. MATSON: The *Saturday Evening Post* has focused considerable attention on this matter. A science reporter described the material of Adams and Naffziger concerned with the results of stellate-ganglion block, and since then many of us have had many pleas to carry out this procedure on persons who have hemiplegias or have been paralytic from weeks to years. The only cases in which my colleagues and I have had favorable results have been those in which the episode occurred under the circumstances Dr. Denny-Brown mentioned, right in our ward. In one case an arteriovenous aneurysm from the carotid artery to the cavernous sinus had been trapped. Right hemiplegia and aphasia developed four or five hours after operation. The ganglion was blocked. In 5 or 10 minutes the patient regained the use of the right side and her speech. The hemiplegia and aphasia recurred four times during the night. The fourth time, perhaps 8 or 10 hours later, the block held, and she did not lose control of speech or of the right side. That is the only case in which we thought that the ganglion block may have affected the vasospasm.

DR. WILLIAM L. HOLT JR.: What is the youngest age in Dr. Denny-Brown's cases? Are Jacksonian or unilateral seizures seen in cases of occlusion of the internal carotid artery? The Lahey clinic saw a 15-year-old girl from our clinic. The diagnosis was not clear. The possibility that she had this condition occurred to me during the presentation.

DR. JAMES L. POPPEN: I should like to ask Dr. Denny-Brown whether the stellate-ganglion block was of the continuous type or consisted of a single injection of 10 to 15 cc. of procaine hydrochloride. I believe that if a procaine block is to be performed in the acute episodes, it should be by the continuous method. My reason for this is my experience with ligation of the internal carotid artery. My colleagues and I have had several cases in which perfusion of the superior cervical ganglion by a continuous drip of procaine after the ligation helped materially, as demonstrated when the injection of procaine was inadvertently stopped. The patient became hemiplegic, and as soon as the procaine was allowed to anesthetize the superior cervical ganglion the hemiplegia disappeared. This has actually happened on several occasions in the same patient. I realize that one is confronted with an entirely different entity in the case of thrombosis of the internal carotid artery. We have had nine patients with thrombosis of the internal carotid artery, and it has been our experience that procaine injection, whether administered at one sitting or by the prolonged method, is not worth while if the hemiplegia has been present a long time.

I should like to take exception to Dr. Denny-Brown's schematic drawing of the arteriogram, showing the ophthalmic artery going into the internal carotid artery. One, of course, sees the ophthalmic artery filled in at least 50% of normal arteriograms, and I agree that collateral circulation can take place by this channel. I object, however, to the statement that the middle meningeal artery can connect with the internal carotid artery; at least, this has not occurred in my personal experience and has not been mentioned in any article in the literature that I have read.

DR. D. DENNY-BROWN: The age range of chronic carotid-artery occlusion was 29 to 74 in our series. Measurements of cerebral blood flow by Kety's method have not shown a significant change following stellate-ganglion block. There appear to be other explanations of any effects obtained. The collateral connections with the external carotid system demonstrated by the arteriogram in the young persons cannot be explained by filling of the vertebral artery. They require considerable time to develop and produce proptosis. The reversed circulation in the ophthalmic artery probably explains the cessation of intermittent blindness when the carotid occlusion ultimately becomes complete. Carbon dioxide is the best dilator.

Clinical Aspects of Diabetic Neuropathy. DR. SAMUEL H. EPSTEIN.

A series of 50 cases of diabetic neuropathy was analyzed from the standpoint of the role of vascular disease. Definite evidences of arteriosclerosis were present in 25 cases, which included instances of general, as well as peripheral, vascular disease. Evidences of local ischemia were found in 12 of these cases. The remaining 25 cases were unassociated with demonstrable vascular disease. The neurologic manifestations in the two groups of cases were the same. Signs and symptoms included impairment of tendon reflexes; paresthesias; pain, both generalized and local; impairment of deep sensibility, as well as loss of superficial pain sense; muscular weakness, often asymmetrical; pupillary abnormalities, and atonic bladder disturbances. Elevation of the total protein content of the cerebrospinal fluid occurred in 70% of the cases and paralleled the severity of the neuropathy.

Diabetic neuropathy from the prognostic standpoint is best classified as two types: (1) that associated with arteriosclerosis and (2) that without demonstrable evidence of vascular disease. The latter type bespeaks a good prognosis, whereas in the former the prognosis is distinctly poor. This applies to the mononeuritic cases, as well as the cases of generalized neuropathy. The patients without arteriosclerosis are usually under 40, in contrast to the older age groups, in which the neuropathy is associated with arteriosclerosis. Prolonged poor regulation of the diabetes in either type plays a role in the precipitation or aggravation of the neuropathy.

DISCUSSION

DR. MADELAINE R. BROWN: I was very much interested in Dr. Epstein's paper. Over 12 to 15 years I have collected 11 patients with diabetic multiple symmetrical polyneuritis, 7 with paralysis of all four extremities, and 4 with paralysis of the legs only. In all of these the paralysis was associated with a high spinal-fluid protein, and three had facial diplegia. Of these three, one died and the condition of the other two improved. The other patients, without signs of cranial-nerve involvement, also slowly improved.

DR. CLEMENS E. BENDA, Arlington, Mass.: Dr. Epstein's paper is very important from a practical point of view. Has he any experience with diabetic neuritis in patients who are not known to have diabetes but have onset of a neuritis? I have seen two cases in which the fasting blood sugar was normal and the urine showed no sugar. However, when a glucose tolerance test was done and blood-sugar determinations were made every two hours over a whole day, the blood sugar rose to 200 or 250 mg. per 100 cc. and stayed at this high level several hours. When these patients were treated with insulin and the high blood sugar was brought under control, the neuritis disappeared gradually, although it took over six months, and the patient's condition generally improved very much. I wonder whether there are not a number of patients with neuritis of unknown origin which is really due to diabetes, and whether in some cases of the so-called alcoholic type the neuritis is in reality diabetic.

DR. WILFRED BLOOMBERG, Framingham, Mass.: My interest was caught by the statement that the patient had an Argyll Robertson pupil. Dr. Epstein has long been interested in neuro-

syphilis and is thoroughly competent in that field. I wish he would amplify this observation for us. Was it actually an Argyll Robertson pupil, meeting all the requirements of that condition in size and in reaction to drugs? Would Dr. Epstein tell us whether he thinks a true Argyll Robertson pupil occurs in anything but neurosyphilis?

DR. SAMUEL H. EPSTEIN: I know of Dr. Brown's interest in this problem. It was she who stimulated my interest in it a dozen years ago. I am glad to know that she has continued her interest. She points out the slowness with which these patients recover and the occurrence of a very high total protein content of the spinal fluid. This had been noted in many series of cases, and in the severest cases the protein will reach 350 or 400 mg. per 100 cc. These cases of diabetic neuropathy are more frequent than is generally seen in the neurologic clinic. When I worked in a diabetic clinic, I was impressed with the great frequency of neurologic disturbances. Figures for diabetic patients with some kind of nervous involvement run as high as 50%.

As to Dr. Benda's question, I do not have any data.

In answer to Dr. Bloomberg's question about the validity of the Argyll Robertson pupil, I can only say that I, too, was skeptical about the occurrence of pupillary abnormalities of the Argyll Robertson type in diabetic patients. I encountered this case, and two others in another series, of 100 cases, I reviewed in a diabetic clinic some years ago. In this case the pupils were small, did not respond to light, but reacted well in accommodation. The reaction to drugs was not tested. It was as true an Argyll Robertson pupil as I have seen in neurosyphilis.

Further Observations on Acute Necrotizing Hemorrhagic Encephalopathy. DR. JOSEPH M. FOLEY and DR. RAYMOND D. ADAMS.

Two cases are presented which, on the basis of their clinical characteristics, appear to represent recoverable forms of acute necrotizing hemorrhagic encephalopathy, a state usually considered to be invariably fatal.

CASE 1.—A boy aged 11 years had a temperature of 105 F., severe headache, signs of meningeal irritation, complete right hemiplegia, and aphasia. Examination of the cerebrospinal fluid revealed 810 polymorphonuclear leucocytes and normal sugar and chloride content. No organisms could be seen on smear or grown on culture. The temperature fell over a period of 1 week, but his aphasia and hemiplegia were complete for 10 days, after which he made a dramatic recovery in the next 2 weeks. Follow-up examinations have revealed no significant evidence of the previous speech and motor disorder, and he has remained in good health for 3½ years.

CASE 2.—A man aged 42 had severe headache; mental confusion, progressing to an agitated delirium, and weakness of the left leg, progressing in 24 hours to complete left hemiplegia. Examination revealed signs of meningeal irritation, complete left hemiplegia, and left hemianopsia. The cerebrospinal fluid showed 1,251 white cells, of which 93% were polymorphonuclear leucocytes. The sugar content was normal. No organisms could be seen on smear or grown on culture. The fever, confusion, and meningeal signs cleared in four days, but the hemiplegia and hemianopsia persisted over two weeks. A dramatic improvement then occurred, so that at the end of another week only a minimal degree of weakness of the left side remained. One month later the only evidence of the disorder was in slightly greater reflex activity on the left side. He has remained well for over 18 months.

The recoverable form of acute necrotizing hemorrhagic encephalopathy should be considered when the following conditions are present: (1) an acute febrile illness with symptoms and signs of meningeal irritation; (2) gross loss of function indicating extensive cerebral or brainstem disorder; (3) rapid and relatively complete recovery, unexpected in view of the completeness of the original loss of function, and (4) polymorphonuclear leucocytosis of the cerebrospinal fluid, with normal sugar and no recoverable organisms.

The Arterial Anastomoses of the Human Brain and Their Importance in the Delimitation of Infarcts. DR. HENRI M. VANDER EECKEN, DR. MILLER FISHER, and DR. RAYMOND D. ADAMS.

Aside from the vessels of the circle of Willis, there are numerous anastomoses on the surface of the brain between the major cerebral and cerebellar arteries. These were recognized and

described in the classic writings of Duret, Heubner, Testut, and Beevor but have not figured prominently in current discussions of vascular disease.

By gross dissection, particularly after injection with a fairly viscous, colored fluid mass, it has been possible to demonstrate communications between the distal branches of the large arteries in the normal brains of 20 adults and 5 children. These anastomoses lie in the meninges, usually within the sulci. As a rule, there are four to six of them between the anterior and the middle cerebral arteries and almost as many between the middle and the posterior and the anterior and the posterior cerebral arteries. In less than half the brains there are several anastomoses between the two anterior cerebral arteries. Several direct communications are always found between the superior, middle, and inferior cerebellar arteries. These loops are 0.2 to 0.6 mm. in diameter. It can be shown that the size and form of a softening consequent to occlusion of a major cerebral or cerebellar artery is at least in part determined by the number, size, and location of the communicating vessels from adjacent arteries.

DISCUSSION

DR. DONALD D. MATSON: In view of the size and number of these anastomoses, why are they not seen in arteriograms? Occasionally one sees the whole system filled at once, but I do not think one recognizes these branches as such.

DR. JAMES L. POPPEN: I suggest that the internal carotid artery filled because the dye passed through the ophthalmic artery, and also through the vertebral artery by the retrograde method. I should like to see the actual arteriograms to determine whether this had taken place.

I believe there is evidence that surgical treatment by removal of the superior and middle sympathetic ganglia has helped these patients. At the same operation the thrombosed internal carotid artery can be resected for microscopic verification and examination. I have been confronted with a case in which an operative anastomosis might have been feasible between the external carotid artery and the distal portions of the internal carotid artery, which were not thrombosed, but I doubt whether such a procedure would be worth while. From previous experience with patients who have had hemiplegia for more than a few minutes, as a result of ligation of the internal carotid artery, I believe that the reopening of arterial channels has no material benefit. The patients who were going to improve did so regardless of whether or not the artery was reopened.

I believe that proper oxygenation is important in the early stages of occlusion of a large vessel.

DR. RAYMOND D. ADAMS: Whether or not these vessels show in an arteriogram would be determined by the set-up in the circulation of the brain. It is not likely that much blood moves as long as the pressure is the same at the two ends. These vessels do not become functional unless the pressure in one circuit falls. They are large enough not to offer much resistance. The problem is probably a simple one in hydraulics. There must be some movement of blood back and forth. The posterior system is seldom filled from the carotid arteries.

In 5 of 20 sections, there were rather sizable connections between the two anterior cerebral arteries, sometimes more than one. Sometimes the one anterior cerebral artery, instead of forming a direct communication, may send a branch off to another hemisphere. This is probably the reason that at times one sees peculiar syndromes when one artery is occluded, and at other times nothing happens after ligation.

DR. D. DENNY-BROWN: Is there any relation to age?

DR. RAYMOND D. ADAMS: Sections have been carried out on normal infant brains and on 20 normal adult brains. In one infant brain, the anastomoses were as large and as numerous as those in adult brains. I suspect they do become more prominent in older brains. In cases in which chronic narrowing of arteries has occurred, anastomotic channels might then become larger and begin to operate.

Fatalities Attributable to Anticonvulsant Drugs: Report of Three Cases. DR. HARRY L. KOZOL.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGIGAL SOCIETY

Bronson S. Ray, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*

Joint Meeting, March 13, 1951

Treatment of Spontaneous Subarachnoid Hemorrhage. DR. LESTER A. MOUNT.

Before definite treatment for subarachnoid hemorrhage can be undertaken, an arteriogram must be made to indicate the best method of therapy. This is usually performed between the 7th and the 10th day after the hemorrhage has occurred.

Surgical therapy consists of a direct intracranial approach to the aneurysm or the reduction of pressure and pulsation within the aneurysm by ligation of the arteries in the neck which supply blood to the aneurysm. In order that one may ligate the arteries in the neck safely, a sufficient amount of collateral circulation must be present. The carotid artery is compressed for 30 minutes in an effort to determine the sufficiency of the collateral circulation. The vertebral artery cannot be compressed without exposing the artery; but ligations are always performed with use of a local anesthetic, and the patient is constantly questioned regarding the development of numbness or weakness and his strength, sensation, and reflexes are examined at five-minute intervals for the first 24 hours after ligation. A tantalum clip is used to occlude the artery; hence, if weakness develops, the clip can immediately be removed. It has been found that the sooner the clip can be removed, the less likely are permanent residuals to occur.

Therapy following the direct intracranial approach to the aneurysm consists of removing the aneurysm; trapping the aneurysm by application of clips on either side of the aneurysm; trapping by application of clips on the internal carotid artery, first in the neck, and then intracranially; clipping the neck of the sac; opening the aneurysm and packing the cavity with muscle; packing muscle around the outside of the wall of the aneurysm, or strategic clipping of the accessible arteries in some cases of arteriovenous aneurysms when the whole vascular abnormality cannot be removed because of the location.

The type of therapy selected is determined on the merits of each case. The mortality rate for patients with spontaneous subarachnoid hemorrhage treated conservatively was 48% in a series of 752 reported cases, in which both recoveries and deaths were included. The mortality rate for the surgically treated patients was 15.4%. This represented 427 cases gathered from the literature and 77 of our own. Of the series gathered from the literature, only those which included deaths as well as recoveries were used.

DISCUSSION

DR. IRVING J. SANDS, Brooklyn: This paper is a milestone in the treatment of subarachnoid hemorrhage. I agree with what Dr. Mount has said, but I think the title should have been "Treatment of Subarachnoid Hemorrhage from Ruptured Aneurysm," for there are other conditions which give subarachnoid hemorrhage. There seems to be a definite agreement that 50% of patients treated conservatively die. About 20% of those who leave the hospital die in five to six years. The difference between 50% and 15% is enough to warrant the type of work which Dr. Mount and his associates have been doing. Arteriography has removed the guesswork as to the cause of subarachnoid bleeding. I have followed several patients who were treated by ligation of the vessels in the neck, and I have not been very happy about the results. The meticulous care which Dr. Mount has given his patients has contributed to the success of his method. I think that the best method is to enter the intracranial cavity and clip the aneurysm when this is possible.

DR. GEORGE H. HYSLOP: I support Dr. Sand's general comment. I should like to have Dr. Mount say a little more as to what determines whether he ligates the common carotid artery with or without intracranial ligation. There is another practical point, I think, which makes surgery advisable. The patient treated conservatively may survive one episode on a

50-50 basis. If that patient survives and stays around New York, where he can get prompt and proper attention the next time he "blows the fuse," luck may be with him. However, if he is somewhere else, away from neurological surgeons, the danger will be that much greater. Some medical neurologists are still afraid to have a surgeon open the skull, and some are still fearful of exposing the spinal cord. It is about time that the competent neurosurgeon be depended on to do a good job.

DR. ALEXANDRA ADLER: May I ask Dr. Mount why he objects to arteriography when the patient is over 60? Is it because complications in older patients are caused by the procedure? Or is it because, even if an aneurysm was found, he would not proceed surgically if the patient was over 60?

DR. IRA COHEN: I should like to add my word of appreciation of a well-considered paper on the treatment of a condition which up to recent years has presented a hopeless situation, hopeless in its not being possible to promise the patient relief from sitting on a volcano, so to speak. I was much interested in the number of arteriovenous aneurysms which Dr. Mount demonstrated in the early arteriograms. It has been my impression that patients who come with moderate recurrent bleeding are more likely to have arteriovenous aneurysms or vascular malformations than the type of aneurysm which Dr. Mount showed, e. g., in the woman with pregnancy. The scheme, as outlined by him and carried out with the care he has given it, will, in proper hands, result in figures such as he has presented and will, I believe, show an even lower mortality state in the future.

DR. RICHARD M. BRICKNER: I should like to ask Dr. Mount for any comments he may have concerning the effect of pregnancy on bleeding, in view of the fact that one of his patients was pregnant.

With Dr. Arthur Ecker, I have seen one such patient. She had had one subarachnoid hemorrhage at the age of about 15. Her second hemorrhage, which was fatal, occurred about 10 years later, during pregnancy.

We questioned whether increased pulse pressure during pregnancy might have helped to induce the second hemorrhage, but we were unable to get enough data to answer this or any associated question. Dr. Ecker was unable to find enough cases in the literature even to permit his determining whether bleeding is especially likely to occur during pregnancy, although we both suspected that it might be.

The subject has obvious importance, and further light on it is very much needed.

DR. BRONSON S. RAY: I should like to ask two questions before Dr. Mount closes. How often has he failed to demonstrate an aneurysm or other lesion when he has made the arteriogram for subarachnoid hemorrhage, and has he had any patients who have had subsequent subarachnoid hemorrhages after ligation of the carotid artery in the neck only?

DR. LESTER A. MOUNT: First, I wish to say that the treatment of these patients was not carried out entirely by myself, but that all the members of the neurosurgical staff of the Neurological Institute did a portion of the operative work involved and here reported.

In answer to Dr. Hyslop's question as to whether or not one should ligate the common carotid artery: We have checked recently the pressure within the internal carotid artery after temporary occlusion of the common carotid artery and after occlusion of the external carotid artery as well, using the Lilly manometer. This procedure allows comparison of the pressure in the internal carotid artery when the common carotid artery is ligated with that when the internal carotid artery is ligated. Dr. William Sweet, of Boston, demonstrated that after ligation of the common carotid artery the flow within the internal carotid artery in some cases was down from the brain and into the external carotid artery, whereas in other cases it was in the reverse direction. We talked with Dr. Jefferson, who stated that even if the flow in the internal carotid artery is down from the brain at the time of the initial ligation, one month later it will be in the reverse direction. We reduced the pressure to the maximum amount in every case, unless there was some specific contraindication. If the pressure was lower within the internal carotid artery after ligation of the common carotid artery than it was after ligation of the internal carotid artery, we ligated the common carotid artery.

In answer to Dr. Adler's question concerning the choice of patients past 60: I should have mentioned that in selected cases arteriographic study is done on patients past the age of 60. With

patients who have a considerable amount of arteriosclerosis, we use thorotrast® instead of iodopyracet (diodrast®) because of the possibility of complications secondary to the arteriographic procedure alone, and the patient may perhaps have more complications following a partial ligation after the age of 60 than before. My colleagues and I are doing some follow-up work on that subject, and in going over our cases recently (the series I have just reported on carried up to 1950, but not beyond) we have tended to conclude that the age limitation may not be a valid one.

In answer to Dr. Brickner's question about pregnancy and aneurysms: We had only the one case, and I am not prepared to answer his question.

In answer to Dr. Ray's question as to how often arteriography has failed to demonstrate the aneurysm: We have had cases in which we have done a complete arteriographic study, and by complete I mean bilateral carotid arteriography and vertebral arteriography, and in which we were unable to demonstrate an aneurysm. The exact percentage I cannot cite, but I should say it is relatively low. We have been particularly interested in patients on whom we have made a complete arteriographic study and failed to demonstrate the site of bleeding. We have had one patient who has bled again.

In answer to Dr. Ray's other question regarding patients with further bleeding after ligation in the neck: We have had two such patients—I mean patients who have left the hospital and have then had a later hemorrhage and died. One had the common and internal carotid arteries ligated, and the other had ligation of the common carotid artery alone. There have been some patients who have had ligation during the time of the bleeding and who have died anyway.

Anxiety and Nor-Epinephrine. Dr. M. Freile Fleetwood and Dr. Oskar Diethelm.

Adrenergic substances in the blood of 30 subjects with varying degrees of anxiety were investigated by quantitative and qualitative pharmacologic methods. The presence of an adrenergic substance was determined by its reaction on the duodenum of the rabbit. It was found that the qualities of these substances corresponded to those of nor-epinephrine because (*a*) the reaction was pronounced on the rat's colon and slight on the rat's uterus, and (*b*) ergotamine failed to block its action on the rabbit's duodenum.

The emotional reactions were studied by one investigator (Dr. Diethelm), while the biochemical studies were done separately by the other (Dr. Fleetwood). A comparison of the psychological and biochemical findings gave a high degree of correlation. The adrenergic substances of epinephrine and nor-epinephrine can be determined quantitatively in epinephrine equivalents, per cubic millimeter.

In mild anxiety, which is recognized clinically by the subject's feeling of mild uneasiness and occasional palpitation, nor-epinephrine varied from 0.25 to 0.75 γ per cubic millimeter. In moderate anxiety (apprehension, occasional anxiety dreams, increased pulse rate, dry mouth, taut throat, moist palms, occasional palpitations, mild shortness of breath, and decreased attention) the nor-epinephrine varied from 1.0 to 2.0 γ. In marked anxiety (apprehension; anxiety, aggressive or hostile; palpitations; dry mouth; taut throat; moist hands; gastric distention; urge to urinate; bowel movement; anxiety dreams; broken sleep; decreased retention, and possible thinking disorders) nor-epinephrine varied from 2.0 to 3.0 γ.

DISCUSSION

Dr. Marcel Goldenberg: We have had some experience with nor-epinephrine at the College of Physicians and Surgeons (Goldenberg, M., and others: *Am. J. Med.* **5**:792 [Dec.] 1948. Goldenberg, M.; Apgar, V.; Deterling, R., and Pines, K. L.: Nor-Epinephrine [Arterenol, Sympathin N] as a Pressor Drug. *J. A. M. A.* **140**:776 [July 2] 1949. Goldenberg, M., and Aranow, H., Jr.: Diagnosis of Pheochromocytoma by the Adrenergic Blocking Action of Benzodioxan, ibid. **143**:1139 [July 29] 1950; Goldenberg, M.; Aranow, H., Jr.; Smith, A., and Mogens, I.: Pheochromocytoma and Essential Hypertension in Vascular Disease, *Arch. Int. Med.* **86**:823 [Dec.] 1950), and it is startling to see how much we disagree with Dr. Fleetwood and Dr. Diethelm. This pertains both to the method used and to the results. The method used was seemingly Gaddum's modification of de Jalon's procedure. This method is tricky enough if plasma is used, but quite unsuitable for whole blood.

Responses to nor-epinephrine are characterized by the lack of reactions referable to the central nervous system, e. g., anxiety, in contrast to those to epinephrine. This has been shown by us

in the work cited above and repeatedly confirmed. We can only say that the results of Drs. Fleetwod and Diethelm do not agree at all with our own findings and the pharmacological work on nor-epinephrine accumulated during the last few years.

DR. M. FREILE FLEETWOOD: We separated the plasma and the red cells. We were aware that West (West, G. B.: *J. Physiol.* **106**:418, 1947) was unable to find nor-epinephrine in the peripheral blood. However, the same author later reported (Mann, M., and West, G. B.: *J Physiol.* **111**:22, 1950) the presence of a substance with the properties of nor-epinephrine in the blood of the hepatic veins, after stimulation of the hepatic nerve.

We are in agreement with West that nor-epinephrine is not present in the blood in the absence of anxiety. However, in patients with anxiety a substance with the properties of nor-epinephrine was found.

The uterus provides the most specific test for epinephrine, and the colon, the most specific test for nor-epinephrine. I shall present a slide that shows the different effects obtained by using these two organs. A sample of blood was taken from a patient in whom Dr. Diethelm had found marked anxiety. The blood of this patient produced a considerable effect on the rat's colon, and no effect could be detected on the rat's uterus, as can be seen in this slide.

We found, as Gaddum reported (Gaddum, J. H.; Peart, W. S., and Vogt, M.: *J. Physiol.* **108**:467, 1949) that some samples of blood presented an interfering substance. In order to investigate whether this interfering substance modified the action of epinephrine, epinephrine was added to blood that gave these effects but was without the adrenergic substance related to anxiety. The effect of blood with epinephrine was the same as that obtained with epinephrine alone, as can be seen in his slide. We concluded that this interfering substance does not modify the quantitative determination of the adrenergic substance.

The Psychodynamics of the Triad Alcoholism, Gambling, and Superstition. DR. IAGO GALDSTON.

The psychodynamics of alcoholism, of gambling, and of superstition were here considered jointly in the conviction that pathologic states, which are puzzling when considered in isolation, may become meaningful when studied in the perspective of a common etiology.

The histories of a male alcoholic, a prostitute, and a male gambler were presented. These three subjects were constitutionally able persons, successful and effective in an appreciable segment of the totality of their life functions. Yet they each suffered from a crippling personality deficiency that robbed them of the full fruits of their endowments and denied them ultimate effectiveness and happiness.

Critical study revealed that the common characteristic of their defective personality structures was the retention within their psychic economy of atavistic components that impeded their effective operation. These persons had suffered some arrest in development, thus presenting the equivalent in the psychiatric field of the better understood and more easily appreciated developmental deficiencies seen in the somatic field. These patients carried into maturity, and incorporated within their adult personality, emotional and psychological dynamisms and relational configurations that belong to the periods of preadolescence and childhood. They retained the child's precausal patterns of comprehending, and dealing, with reality and with experience.

These patients suffered early and severe deprivations in their affect relations with their parents and with their siblings, relations essential to a healthy development through infancy, childhood, adolescence, and youth. They behaved as though harking back to that early period at which they suffered the arresting deprivation. There they appeared to be compulsively fixated, and from thence they semed unable to advance.

DISCUSSION

DR. SANDOR RADO: Dr. Galdston proposed the taking of a fresh view of alcoholism, gambling, and superstition: He studied his patients, rather than the material accumulated in the library. This is a highly commendable approach, notably in psychiatry. One could only wish that it might be adopted by younger men in the field. Independent observation, unhampered by a stereotyped outlook, is precisely what is needed.

The prevalence of magical thinking in alcoholism, gambling, and superstition has been stressed by various observers. The difficulty with the significance of this finding is that the same kind of magical thinking is seen also in a large variety of other psychiatric disorders. Some of us feel that magical thinking is not a causative factor, but, rather, a factor brought into play by a process of miscarried repair. This attempt at repair draws on a resource, the belief in omnipotence, which is fundamental to the psychodynamic organization of our species.

Dr. Galdston traced the common feature of these three conditions to what Piaget called the precausal thinking of the child. However, this concept of Piaget is controversial. Another view is that the child's need for causality is even greater than that of the adult. A pathologic state may then throw the adult back to the infantile level; for instance, Bleuler found the alcoholic's need for causality to be increased. In this view, the need itself arises at an early date, but maturation changes the ways in which it is supplied. In children and preliterate man, and again in alcoholics and patients with other psychiatric disorders, the need for causality is fully satisfied by a primitive mode of thought, the various aspects of which have been characterized as animistic, emotion-bound, autistic, dereistic, and magical. In the healthy adult, on the other hand, it tends to be satisfied only by reasoned constructions based on evidence, i. e., by a mode of thought that is both realistic and logical. It is a fair guess that the various observers, including Dr. Galdston, see the same fact, but we must still toil with the vexing task of finding an adequate language for its description.

Lack of time prevents me from discussing the many fine observations contained in Dr. Galdston's case reports. These details have enhanced the pleasure of listening to his interesting presentation.

Clinical Evaluation of Fifty Lobotomized Patients. DR. ARNOLD DAVIDSON.

Fifty patients on whom prefrontal lobotomies were done at Manhattan State Hospital were evaluated clinically in an effort to determine the result of the procedure. There were three deaths—one during anesthesia, one due to pulmonary embolus, and one due to bronchopneumonia. Forty-seven patients, aged 24 to 63, were followed from 8 to 27 months after operation. They all satisfied the following criteria for operation: (1) duration of psychosis of two years or more; (2) previous treatment—either insulin or electric-shock treatment or both; (3) no evidence of improvement after treatment; (4) persistence, preferably despite physiological treatment and psychotherapy, of a compulsive-obsessive, aggressive, homicidal, suicidal, assaultive, negativistic, or disturbed state; (5) good physical condition.

The diagnoses were as follows: involutional psychosis, paranoid type, 1; manic-depressive psychosis, 2; schizophrenia, hebephrenic type, 10; schizophrenia, catatonic type, 13; schizophrenia, paranoid type, 24. The group was divided into 36 hyperkinetic patients (assaultive, destructive, homicidal, suicidal, obsessive-compulsive or aggressive, especially those requiring frequent sedation or restraint) and 14 nonhyperkinetic patients (primarily negativistic and withdrawn, requiring a great deal of nursing care). The results were personally evaluated by the author after repeated interviews with patients, attendants, nurses, ward physicians, and relatives, and patients were divided into those showing no improvement (no discernible benefit from operation); improvement (ability to make better contact with their environment and to care for themselves more efficiently; loss of aggressive behavior); great improvement (much improved behavior; better contact with environment; ability to do ward work or to take part in occupational therapy; in general, so much improvement that the patient was either out of the hospital or eligible for convalescent care). The results were as follows: great improvement, 11 patients; improvement, 23 patients; no improvement, 13 patients. The complications were few; convulsions were easily controlled in the nine patients in whom they developed. Patients routinely received phenobarbital and vitamin supplements for three months after operation. Psychological studies were attempted, but only on 28 patients could scorable Rorschach data be obtained. The correlation between Rorschach and clinical findings was poor. The author believed that for those patients with a history of long-standing psychosis and hospitalization and no response to treatment, a radical procedure, such as lobotomy, was justified, and that the results exceeded expectations and made the procedure eminently worth while.

DISCUSSION

DR. LEO M. DAVIDOFF: The selection of patients, the decision for operation, and the postoperative follow-up study were made by the psychiatrists at the hospital. The surgical program was set up at the Manhattan State Hospital, and the majority of the operations were done by Dr. E. H. Feiring and Dr. K. M. Gang. The procedure was standardized by the use of a leucotome, described by Brenner and myself (*A. Res. Nerv. & Ment. Dis., Proc.* **27**:638, 1948). The instrument has a rail attached to the skull through small stab incisions and screwed into place by three small screws, and a carriage, which can pass on the rail. The lateral view shows serrations; the top of the carriage carries the leucotome. It is attached to the lower part by a series of teeth, which are spaced at such distance from one another that the movement from one tooth to the next allows the leucotome to be inserted into the brain and overlap by a small amount the previous incision. Thus, instead of making a sweep, as with most leucotomes, we do these leucotomies by a series of stab incisions, each one overlapping the other a little, so that the whole area is incised, and we avoid tearing small vessels, such as are encountered when a sweep is made. The advantage of the rail is that the plane of the incision is always exact; and, finally, we find that the precision of the plane of incision and the use of stab incisions result in each operation being done very nearly like the others. There is also an arrangement, a flange, which is so constructed that when the projection from the leucotome strikes it at different places, the end of the leucotome cannot pass beyond the midline; thus, a series of stab incisions occur at different distances from the point of incision, but always at a line within 0.5 cm. of the midline. We feel that this is an additional safety factor in controlling operation.

May I ask Dr. Davidson whether he has noted any considerable difference in the results in the two groups of patients which he has classified as hyperkinetic and akinetic?

DR. PAUL H. HOCH: Dr. Davidson's paper raised many interesting points: this first is the selection of the patients for operation. It again confirms the belief that patients who show a strong emotional component—a rather active emotional behavior—fare much better with the operation than those who are apathetic, blunted, or completely devoid of emotional response. This is important, for patients are still selected for operation in whom, practically speaking, the emotional life is burned out. These patients usually do not respond well to lobotomy, and I do not believe they should be operated on. I am not too pleased with the terms "hyperkinetic" and "akinetic," for these terms are usually used to designate the results of other syndromes, but I believe that patients who show a strong emotional display before the operation do fare better. Incidentally, negativistic patients also fare well because negativism is an active pattern, and not a passive one. The responses to the operation may be graded as follows: Patients who show tension, anxiety, and obsessive-compulsive behavior respond best; second come those with depressive psychoses; third, those with delusions or hallucinations, and fourth, and most poorly, those with strong disintegration patterns. These results would indicate that psychoneurotic or schizophrenic patients respond much better to the operation than do patients who show deterioration.

The improvement in Dr. Davidson's series corresponds to that reported by others. About 20 to 25% of his patients showed good improvement. In addition, a number were listed as improved. In evaluating therapeutic results my colleagues and I concentrate mainly on the patients who show great improvement. All statistics in psychiatry are cluttered up with "improved" patients. This designation is often meaningless, for oscillation in the patient's condition is such that on one day he appears to be improved and on another day he does not. Dr. Davidson demonstrated how difficult it is to appraise a not-too-well-defined improvement by discussing patients who were judged by the staff to show no improvement and by the relatives to be improved, even though not conspicuously so.

Dr. Davidson brought out the important point of the correlation of clinical observations and psychological tests. Actually, psychological tests do not reveal very much after lobotomy or similar operations. Nevertheless, a constant effort is made to use the Rorschach or similar tests to appraise operative results. However, the test is able to show only that a conflictual situation is present, not how far the patient is now able to handle the conflict. It is of great importance that the Rorschach test reveals that the basic structure of the neurosis or psychosis is the same after operation. By giving the patient certain drugs, such as mescaline, before and after the

operation, we were able to demonstrate the same thing. The conflictual situations, the anxiety, could be reactivated in the patient, but not to the same extent as before the operation. This indicates that, even though the conflicts remain, the quantity of the emotional charge is reduced, and the patient is then able to handle the situation constructively. The Rorschach test shows the basic structure, but does not reveal the quantitative reduction reliably.

I should like to ask Dr. Davidson two questions: First, it is interesting to note that in the material presented no side-effects, such as personality damage, are shown. We have found that, though lobotomy is an effective form of treatment, personality damage does occur in a number of patients. I am also interested in knowing why such damage does not appear in his interpretation. I should also like to ask why he uses phenobarbital, and not diphenylhydantoin, to prevent convulsive seizures.

DR. J. LAWRENCE POOL: I should like to congratulate Dr. Davidson and to say that his careful clinical evaluation of these lobotomized patients is of the utmost interest and importance. I should like to mention the possibility of other operations, for reasons to be enumerated briefly. The psychiatrist selecting an operation, such as lobotomy or topectomy, should be aware of the potential complications and operative death rate. More than 250 bifrontal topectomies have now been done by Dr. Davidson and his associates, without a single operative death, whereas deaths following lobotomy range from 1 to 18 per 100 operations, with an average mortality rate of 3%.

As to complications, postoperative convulsive seizures have been reported in 3 to 35% of patients after frontal lobotomy, with an average of 12.3%, or 18% in the series reported tonight. In a consecutive series of 75 patients with one-stage, nonproject topectomies performed by the speaker, of whom 60% have been followed for two years and 18 for three years or more, the incidence of seizures was 13.3%. Post-topectomy hematoma occurred in 3% of this series, but in each instance the condition was treated by prompt evacuation, with no ill effects. According to published accounts, however, there are a number of deaths due to hemorrhage after lobotomy.

Since the over-all clinical results of topectomy are comparable to those of lobotomy, and since the incidence of seizures after lobotomy is about the same as that after topectomy, the latter seems preferable, since it carries less risk of operative death.

I should like to ask Dr. Davidson about the nature of the postlobotomy seizures, for I am interested in those occurring after topectomy. I should also like to know what mechanism he ascribes to the production of these seizures.

DR. MORTIMER OSTOW: A patient who consulted me two days ago comes to mind; he is a man of 54 who had his first schizophrenic breakdown at the age of 19. About one-third of his adult life has been spent in psychiatric hospitals. In the remaining two-thirds of his adult life he has managed to achieve an enviable scientific reputation; he has a long biography in "Who's Who." He is a man who has contributed his name to important scientific journals. Five years ago he fell sick; he had a long series of electric shock treatments, after which he secluded himself in his apartment and permitted no visitors. I think these conditions satisfy all the criteria set up by Dr. Davidson. Four weeks ago he shaved his beard, washed his face, and emerged from his apartment. He was immediately appointed as professor to a university faculty, teaching graduate courses. He sent a few papers he had written during the past five years to a scientific journal and immediately received letters of gratitude from the editor for submitting them. He has now come to receive psychotherapy. I must say I am glad he did not find his way to Manhattan State Hospital, where he might have been subjected to operation, and reported as "an improved psychotic."

DR. THEODORE R. ROBIE: In view of the fact that one cannot get the family's permission for operation in many of the cases in which the illness is prolonged and the patients are difficult to manage, particularly those who are homicidal, and who thus may harm other patients, nurses or attendants in the hospital, have you tried to operate without the family's permission?

DR. OSKAR DIETHELM: I should like to ask by what standard the patients' status was judged improved or unimproved. Two months ago I saw 14 or 15 patients at the Montrose Veterans Hospital who had been considered unimproved. The majority had been operated on by Dr. Davidoff several years before. All but one had shown some improvement, and some showed considerable improvement along certain lines and fitted better into the therapeutic and social situation of the hospital. I had not quite anticipated the result. When we speak of the

damage in lobotomy, we must consider that we do not know what to expect or how to test for it. Many symptoms, which in the past have been considered indicative of schizophrenia or other type of deterioration, are rarely observed in the present medical and cultural development of psychiatry. We should evaluate carefully and state clearly what the signs of improvement are and in what way a patient's condition has not improved or is actually worse.

DR. HERMAN C. B. DENBER: Dr. Davidson is to be congratulated on having assembled and presented these data to the society. Dr. Ostow should be congratulated, too, on knowing such an eminent scientist. His report illustrates the fallacy which permeates psychiatric literature, namely, that of drawing conclusions from one case. Obviously, one should not be guided by isolated case reports. I am not enough of a mathematician to state whether these 50 cases in themselves have statistical validity, but the fact remains that they have much greater significance than a single case. Perhaps it is fortunate that Dr. Ostow's patient did not find his way to our hospital. If ever psychiatry and psychoanalysis are to achieve their rightful place among the other fields of medicine, the emphasis must be shifted to group studies, such as Dr. Davidson has presented.

DR. ARNOLD DAVIDSON: I think Dr. Hoch answered Dr. Davidoff's question about the results so far as the hyperkinetic and akinetic patients are concerned. The results are much better for the hyperkinetic patients, but every once in a while a patient placed in the akinetic group shows truly remarkable improvement. Dr. Hoch's interpretation of negativism being a positive thing is another explanation of the situation.

Dr. Hoch asked about personality damage. That question has been brought up in previous discussions on the same material; we did not start with any Einsteins; we did not do any damage to the extent of impairing great intellects. One must keep in mind our case material: these patients had no personality. We obtained Rorschach findings on 28 patients; the other 22 did not have enough contact with reality to enable one to get Rorschach findings; so one cannot talk about personality changes in case material of this type.

As to the prophylactic use of phenobarbital, the procedure was set in motion by others; I do not know why the drug should be used, except for its ready availability.

Dr. Pool asked about the seizures. They were all in the nature of grand-mal attacks. There was nothing focal about them—and I witnessed most of them. I do not know the reason for the seizures, probably a focal irritation.

Dr. Ostow's discussion of his case is very interesting, but we are reporting on 50 patients from our material. They are patients who have had long periods of psychosis, long periods of hospitalization, treatments of various kinds, and, most of them, previous hospitalizations in other institutions. There was no personality to deal with. They were problems in ordinary custodial care; so I think that something radical, like a lobotomy, was justified, since nothing less would do much good.

In regard to doing lobotomies without permission, that is not legal and would not be done.

Dr. Diethelm raised the point of what we consider improvement and what no improvement. The decision is based purely on our own judgment, after we have seen the patient many times and have interviewed the ward personnel and the doctors and nurses, so that we have a total evaluation of the whole situation. It is a clinical report on whether or not the patient has made any kind of improvement after operation. We do not quibble over terms, and we do not want too much read into them. We admit that all the patients, even the much improved, retained their psychoses. These 50 patients were "hell-raisers," who presented problems in care and took up the time of the doctors and personnel. We feel that the results so far as that aspect is concerned are eminently successful. Eleven showed much improvement, and 23 showed improvement, since they did not require frequent sedation or the attention of ward personnel in taking them to the toilet. We were not so much interested in psychological testing as in the clinical improvement of these patients.

News and Comment

FIFTH INTERNATIONAL NEUROLOGICAL CONGRESS

The Fifth International Neurological Congress will be held in Lisbon, Portugal, during the middle of September, 1953. The exact dates of the Congress will be determined later, and further announcement will be made. Special attention will be paid to the neurosurgical aspects of the symposia. In accordance with the usual custom, one day will be devoted to excursions in the vicinity of Lisbon.

A meeting in commemoration of the birth of Ramon y Cajal will be held in Madrid immediately after the conclusion of the Congress. This meeting will be sponsored by the Spanish neuropsychiatrists. Plans as to the program of the meeting, those eligible to attend it, the place and dates of the meeting, and other details will be elaborated by the Spanish neuropsychiatrists. An announcement as to these matters will be made at a later date.

The officers of the Fifth International Neurological Congress are as follows: honorary presidents, Sir Charles Sherrington, Dr. Gordon Holmes, Prof. Georges Guillain, Dr. André-Thomas, Prof. T. Alajouanine, Prof. A. Egas Moniz; honorary vice-president, Prof. A. Austregesilo; president, Prof. Antonio Flores; secretary general, Prof. Almeida Lima, Hospital Julio de Matos, 53 Avenida Brasil, Lisbon; treasurer, Dr. J. Imaginario; assistant treasurer, Dr. V. Ramos. The local secretary and assistant secretary and the editor and assistant editors of the *Proceedings* of the Congress will be appointed at a later date.

The vice-presidents, representing various constituent countries, are as follows: Belgium, Prof. van Gehuchten; Brazil, Prof. Deolindo Couto; Chile, Prof. A. Asenjo; Denmark, Prof. Knud Krabbe; France, Prof. Raymond Garcin; Great Britain, Prof. F. M. R. Walshe; Netherlands, Prof. W. Sillevis Smitt; Italy, Prof. L. de Lisi; Norway, Prof. Monrad-Krohn; Spain, Prof. J. Lopez Ibor; Sweden, Prof. Nils Antoni; Switzerland, Prof. F. Luthy; Turkey, Prof. Sukru Aksel; United States, Prof. Henry Alsop Riley. Other vice-presidents, to represent national groups not present at the meeting of the Executive Committee, will be appointed later. A vice-presidential position has been reserved for each country which is entitled to such representation. The national committees will be consulted in regard to the designation of vice-presidents from the national neurological groups. It was decided that Germany and Japan should be invited to participate in the Congress of 1953.

The Portuguese national committee will be composed of Drs. Flores, Correia de Oliveira, Almeida Lima, Imaginario, and Ramos, and others who may be added.

The Executive Committee, which met in Lisbon in July, 1951, selected three topics for the symposia of the Congress. The subject of each symposium and the persons entrusted with the preparation of these special topics are as follows: Cerebrovascular Conditions (two sessions), Drs. Egas Moniz and Alajouanine; The Parietal Lobe, Dr. Walshe; Metabolic Diseases of the Nervous System, Dr. van Bogaert.

The program for each of these symposia will be prepared by the chairman in charge, and about four invited speakers will be selected to present various aspects of the subject. Twenty minutes will be allowed to each invited speaker for the presentation of his paper.

Individual members of the Congress may discuss any one of these topics if application is made in advance in writing to the secretary general. Five minutes will be allowed for such discussions.

After the prepared discussions, free discussions will be permitted from the floor, with a limit of five minutes for each discusser.

Afternoon sessions will be arranged to permit the presentation of papers on miscellaneous subjects, which will be grouped so far as possible in accordance with the subject matter of the communications. Ten minutes will be permitted for the presentation of each one of these papers on miscellaneous subjects. A sufficient number of sessions will be arranged to allow for the presentation of all contributions admitted to the program by the program committee. A

request by United States members for a place on the program for these 10-minute papers must be submitted to the secretary of the United States committee, accompanied by an abstract in quadruplicate, not exceeding 200 words, before Jan. 15, 1953. Only active members of the Congress may submit titles to be presented during the sessions for miscellaneous communications. Each active member may present one paper. Nonmembers will be allowed to discuss presentations only if invited by the presiding officer of the session.

The official languages in which papers may be presented are English, French, Italian, Portuguese, and Spanish.

Membership in the Congress will consist of active, associate, and adjunct members. Applicants for active membership must belong to some national or local neurological psychiatric, neuropsychiatric, or neurosurgical association or society. The fee for active membership will be $15.

Physicians in other specialties and persons engaged in fields or scientific activity associated with neurology, psychiatry, or neurological surgery may apply for associate membership. The fee for associate membership will be $10.

Members of the families of members, and nonmedical persons interested in the Congress, may apply for adjunct membership. The fee for adjunct membership will be $5.

Application blanks for United States nationals for all types of membership in the Congress may be obtained by writing to the secretary of the committee for the United States, Dr. H. Houston Merritt, Neurological Institute, 700 West 168th St., New York 32.

Each application for active membership must present endorsement by some national or recognized local neuropsychiatric or neurosurgical organization or by a neurologist or psychiatrist known to members of the United States committee.

Canadian neurologists and psychiatrists and other Canadians interested in attending the Congress should communicate with Dr. J. Allan Walters, Medical Arts Building, Toronto, Canada.

The American Express Company has been chosen as the official travel agency for the Fifth International Neurological Congress. In order to obtain the most satisfactory results, arrangements for travel or for hotel accommodations should be made through the American Express Company. Arrangements may, of course, be made through any travel agency, but in order to ensure the most satisfactory results, it is advised that the recognized travel agency be employed for these purposes. Early application for room reservations should be made.

An effort will be made to reserve a sufficient number of various types of staterooms on some eastbound steamship sailing at the end of August or the early part of September. Similar arrangements will be made for the westbound passage toward the end of September. In all probability, special tours through the various parts of Portugal and adjacent countries will be arranged by the American Express Company for those wishing to take advantage of such facilities.

The support of the Congress will be provided by the membership fees and an appropriation from the national neurological association of each of the constituent countries, representing the equivalent of $1 for each member of the national organization.

The proceedings of the Congress will be published. They will consist of abstracts of presentations and discussions, together with other pertinent details concerned with the conduct of the Fifth Congress.

As no title or abstract will be accepted by the United States committee unless at the time of submission the author is an active member of the Congress, an application blank for membership properly filled out, together with check in payment of the membership fee, should precede or acompany the title and abstract and should be addressed to Dr. H. Houston Merritt, Neurological Institute, New York 32.

Committee for the United States, Fifth International Neurological Congress: Henry Alsop Riley, chairman; H. Houston Merritt, secretary; John F. Fulton; Foster Kennedy; S. Bernard Wortis; Walter Freeman; Francis C. Grant.

Obituaries

SAMUEL WARREN HAMILTON
1878-1951

Dr. Hamilton never got a chance to retire. He was much too valuable. When the Public Health Service reluctantly let him go from the Mental Hospital Survey Committee, Essex County, New Jersey drafted him to be director of their Overbrook Hospital at Cedar Grove. In 1950 he made what he thought was a final attempt at retiring. He went up to his beloved native state of Vermont to look forward to a life of ease. But it was not to be. The governor of Vermont induced him to make a survey of the state institutions. It was while working on this survey that he died suddenly of a cardiac attack, while in the office of the superintendent of the Rutland State Women's Reformatory. He died in the front line of duty, which, to him, was always the most important thing in life.

Samuel W. Hamilton was born in Brandon, Vt. in 1878, the son, grandson and great-grandson of physicians. The medical background was ingrained in him. His maternal grandfather was a dentist. Shortly after his birth his father died, at 27 years of age, as the result of a bite by a diphtheria patient. His mother taught music to support her only child and gave him the background of intense honesty which was to be his outstanding characteristic for the whole of his life. People who knew him only slightly will remember him for that.

Dr. Hamilton attended the public schools of Vermont and was graduated from the Rutland High School before he entered the University of Vermont. Graduating from there with the degree of Bachelor of Arts in 1898, he immediately entered the College of Physicians and Surgeons in New York and received the degree of Doctor of Medicine in 1903. As a student he was interested in the welfare of others and was a prominent member of the Y.M.C.A. of the college.

After graduation he served a year's internship in the New York Children's Hospital and then a year in the New York Lying-In Hospital. By this time he had made up his mind that psychiatry was what he wanted to practice; so in 1905 he went to the Manhattan State Hospital, on Ward's Island. For the next twelve years he devoted himself to the state hospital service in New York City and in Utica. In 1917, when the New York City Police Psychopathic Laboratory was established, Hamilton became the director, and he ran the laboratory until he entered the Army in the same year.

His service in the Army in World War I was a brilliant success, first as psychiatrist to the 42nd Division, then the 1st Corps and, finally, to the Third Army. He had come out of the narrow environment of the state hospitals and met many men of different interests. He made friends for himself and for psychiatry wherever he went and was one of the pioneer group who made the Army aware of what psychiatry had to offer them.

Leaving the Army, he went to the Philadelphia Hospital for Mental Diseases as medical director until 1923, when he was appointed assistant medical director of

Bloomingdale Hospital. There he stayed until 1936, serving at the same time with the National Committee for Mental Hygiene in its hospital department.

In 1936 the Mental Hospital Survey Committee was founded by a number of organizations to conduct surveys of mental hospitals of the country and Canada, and Hamilton was the natural choice for director of that survey. This started him on a roving life, which took him all over the country. His job was to find out the truth about hospitals, which is the sort of thing that seldom makes a man popular. But Hamilton was singularly gifted for that work. His fairness and scrupulous honesty were apparent to all with whom he came in contact. His able reports, with no sensationalism and no punches held back, were a monument to his ability and integrity. Governors and legislatures all over the country read his reports and acted on them. The most striking example of the value of his work was manifested in the unprecedented action of Governor Youngdahl, of Minnesota, who recently appointed him Honorary Commissioner of Mental Health of the State of Minnesota.

When the United States Health Service took over the Mental Hospital Survey Committee, they were glad to take Hamilton along with them, and he continued his brilliant and valuable surveys until he was retired, in 1947. Then came the directorship of the Essex County Overbrook Hospital, the move to Burlington, and the sudden death in the midst of one of those surveys that he made with such brilliance and devotion.

Dr. Hamilton did considerable writing and lecturing, mostly in connection with the things he had turned up in his surveys. He was a member of many psychiatric societies. In 1938 he was president of the American Psychopathological Association and at the peak of his career, in 1946, was president of the American Psychiatric Association.

In 1946 his Alma Mater, the University of Vermont, awarded him the degree of Sc.D. (honoris causa).

Sam Hamilton was a wonderful fellow. Honesty was practically a vice with him, and about the only vice he ever had. A loyal friend, he was the kind of fellow one liked to be with. He was always interested in everything with which he came in contact. He always had something interesting to say, and he was just as good a listener as a talker. A unique person, he will be long remembered by his friends.

LOUIS CASAMAJOR, M.D.

Book Reviews

Health and Human Relations in Germany. Price, $1. Pp. 207. The Josiah Macy, Jr. Foundation, Editors, 565 Park Ave., New York 21, 1950.

This book, a report of the conference on Problems of Health and Human Relations in Germany, held in Princeton, N. J., June 26 to 30, 1950, has a unique value, due in part to the excellent organization of its material. The reader is given a sense of being in on timely and significant events with (as is not possible in accounts by reporters) an intelligent assessment of these happenings by professional men and women concerned with the needs, met and unmet, of postwar Germany.

A foreword by Frank Fremont-Smith, M.D., medical director of the Josiah Macy, Jr. Foundation, states the general objectives of the meeting: "For some years the Macy Foundation has had a special interest in the problem of communication.... Experience shows that the principles of human relations, applied in groups with a common purpose, aid in communication and further scientific advance. A logical next step is to find practical ways in which the same principles may be utilized within social institutions and by government agencies on the national and international levels to improve communications between the peoples of the world." Upon this clear statement of purpose, the conference procedure was based.

Composed of thirty-six professional workers (with more than half attending as individuals or representatives of private organizations) the group was made up mainly of psychiatrists, psychologists, social service workers, educators, and sociologists. Besides French and British representatives, there were four German members. All participants had a background of interest in German problems.

The conference was sponsored by the Josiah Macy, Jr. Foundation, with the cooperation of the United States Children's Bureau and the National Institute of Mental Health, and with the approval of the Department of State. Jean W. Conti, of the Macy Foundation, was in charge of writing the report, proceeds from its sale being devoted to furthering the work of the World Federation for Mental Health.

The work of the conference was divided among three committees. "German Culture and Personality" was the subject undertaken by Committee I; "Professional Developments in Psychiatry, Social Sciences, and Education" by Committee II; and "Integration of the German Culture with Itself and into European and World Cultures" by Committee III.

Addressing itself primarily to problems which Americans and Germans have worked on together since the war, Committee I noted certain cleavages in cultural and family relationships which have tended to be detrimental in Germany. How can acceptance of the authority of the father as arbiter in the family group be modified? What educational methods would bring about more give-and-take between teachers and students, and teachers and parents? How can women be encouraged to participate more spontaneously in community projects? Stressing the fact that changes cannot be imposed upon the German people (while admitting that such attempts, unfortunately, have been made), members of this committee enumerated, and recommended for further study, developments which have been favorably received in Germany. Among them are neighborhood youth centers; improved status of labor in industrial relations; scholarships offered by trade unions for working students; adult education; less formal methods of education, with more emphasis on the teaching of the social sciences, and cooperation of German church groups.

Committee II placed emphasis upon aiding the professional services: education, psychiatry, clinical psychology, and social welfare. It was the members' opinion that there should be better physical facilities and equipment in German schools. In order that psychiatry be more closely related to the public, it was recommended that there be established health centers, outpatient set-ups, and guidance clinics, and that greater specialized training be provided for social-service workers and affiliated with the work of the centers. Exchange of personnel specializing in educational and clinical psychology with the United States and other countries was favored. Supplementary teaching centers in the child-guidance field, neighborhood and youth centers, and

community programs were also suggested. Clearing houses of information on human relations as undertaken in Germany were urged as a means for the integration of knowledge bearing upon mental health and interprofessional effort.

Committee III considered such subjects relating to postwar Germany as its youth, types of personality structure, problems of communication, and love and hate as motivating factors in human relations. The committee judged these problems relatively, and as not confined to Germany. United Nations Educational, Scientific and Cultural Organization's plan for information centers in Germany was noted as a desirable way to help the half-million homeless people 18 and 23 years old to express their reactions to their problems. Suspicion, intolerance, and diminished capacity for feeling were cited as barriers to understanding between individuals and groups. The Exchange-of-Persons program was praised as a means for overcoming many of these barriers, but it was brought out that frequently the conformist type of German was chosen to participate, rather than the individualist or leader. It was suggested that an important study might be centered on the status of German women bringing up fatherless children, as well as on the economic difficulties women face as wage earners. This committee commended the special contributions of the Unitarian Service Committee and the Friends' group activities in Germany and urged that these be taken as examples of "the effective interrelationship of ideas and actions."

Individual participants in the conference frequently remarked on the necessity for maintaining a relationship between ideas and actions in a program for Germany. As one member said, "Many people in Germany are so taken up with the struggle to live that they can think of nothing else." In the report of Committee III, the following approach was favored: "In the community organization movement in America, techniques have been developed for helping people to overcome suspicion of each other. One device, for example, is to have areas of interest, rather than specific organizations, represented on planning bodies."

In the opinion of the reviewer, there has, perhaps, been too great emphasis placed upon the solutions provided by educational and cultural means, and not enough upon the problems of actual human needs. Homeless refugees must unavoidably have as their major concern their homelessness. Until this issue is adequately met, the calmness necessary for understanding and tolerance will be unattainable, however expert guidance in human relations may be. Is it not possible that the acceptance of a common need as an "area of interest" constitutes one of the factors of success in the work of the Friends and Unitarians?

However, this observation on emphasis in no way invalidates the vital work accomplished by the Princeton conference. In his opening address, John R. Rees, M.D., director of the World Federation for Mental Health, said: "Many specialists have undertaken surveys and projects aimed at repairing the damage to German minds and bodies done by the war and the period of Nazi rule.... Too frequently they worked in complete isolation from one another."

Programs like Point Four are based upon the need for technical and material assistance in underdeveloped countries. An organization like UNESCO strives for increased understanding through cultural exchange and communication.

The synthesis of these two approaches is surely one of the great hopes of the future. Success is brought closer by meetings such as the one held at Princeton, where men and women, representing different professions and nations, proceed with patience and tolerance to pool their information and experience for the sake of a common goal, and consolidate their gains in understanding with plans for further action. Both as a historical record and as a guide for social scientists and government leaders, this report is a fundamental contribution.

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